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ORIGINAL RESEARCH

# Association of the Early Response to an Oral Shape-Shifting Superabsorbent Hydrogel Capsule With Weight Loss

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## ABSTRACT

Early response (ER) to treatment is predictive of longer-term weight loss. In this post hoc analysis, ER to an oral shape-shifting superabsorbent hydrogel capsule (Epitomee) combined with a lifestyle intervention was compared to placebo combined with a lifestyle intervention. Participants (age = 48.5 ± 12.5 and 48.6 ± 12.4; BMI = 34.1 ± 3.3 and 33.7 ± 3.4, in the Epitomee and placebo groups, respectively) were randomised to Epitomee ($N = 138$) or placebo ($N = 141$) with lifestyle intervention. Analyses included body weight measurements taken at baseline, week 8, and week 24. Of the 279 participants enrolled in the study, 250 (90% of the ITT population) provided weight data, including 124 participants in the Epitomee group and 126 in the placebo group. Participants with missing weight data at week 24 were classified as non-responders. Early response (ER) was defined as a weight loss of ≥ 2% at week 8. Weight loss at week 24 was greater in ER to Epitomee compared to placebo (9.3% ± 6.0% vs. 6.9% ± 4.3%; $p < 0.0001$). The odds ratio for ER to achieve > 5% weight loss at week 24 was 4.10 (95% CI: 1.02, 16.46) for Epitomee and 2.38 (95% CI: 0.62, 9.21) for placebo. A greater proportion of ER to Epitomee, compared to placebo, achieved > 5% (76% vs. 62%; $p = 0.0472$), ≥ 7% (61% vs. 38%; $p < 0.0045$) and ≥ 10% (39% vs. 17%; $p < 0.0025$) weight loss at week 24. ER response to Epitomee was associated with greater weight loss at 24 weeks compared to placebo. Monitoring ER to Epitomee and titrating treatment based on ER may enhance weight loss.

## 1 | Introduction

The Epitomee capsule is a minimally invasive, oral, self-administered medical device for weight management in patients with overweight or obesity [1, 2]. The Epitomee capsule was recently shown to improve mean weight loss in a 24-week pivotal trial compared to placebo (−6.6% ± 6.5% vs. −S4.6% ± 4.7%) when coupled with a lifestyle intervention. Moreover, 56% of Epitomee capsule-treated participants versus 44% of those receiving placebo achieved ≥ 5% weight loss at 24 weeks; 27% of Epitomee capsule-treated versus 11% of placebo-treated participants achieved ≥ 10% weight reduction [3]. However, inter-individual variability in weight loss was observed in both the Epitomee and placebo groups, which warrants additional

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**Summary**

- What is already known about this subject?
  - The Epitomee capsule is a novel, oral medical device for weight loss, consisting of super-absorbent, pharmaceutical-grade polymers and bonding materials that self-expand in the stomach to form a triangular gel scaffold.
  - In the RESET prospective, randomised, double-blind, placebo-controlled study in participants with overweight or obesity, the Epitomee capsule combined with a lifestyle intervention induced a significantly greater mean percentage reduction in baseline body weight than placebo at week 24 and had a favourable safety profile. Epitomee combined with lifestyle treatment was associated with improved cardiometabolic risk factors and satiety.
- What this study adds?
  - In this RESET post hoc analysis, response to treatment at week 8 of ≥2% was predictive of week 24 weight loss in both participants treated with Epitomee combined with a lifestyle intervention and placebo plus lifestyle intervention.
  - Early responders to the Epitomee combined with lifestyle treatment, compared to those using a placebo with lifestyle, had significantly greater weight loss at week 24 (−9.3% ± 6.0% vs. −6.9% ± 4.3%; $p < 0.0001$) and were significantly more likely to achieve weight losses of at least 7% and 10% at 24 weeks.
  - Evaluating early response of ≥2% at 8 weeks can inform a decision to continue or change treatment with Epitomee and lifestyle intervention in patients who seek weight loss to improve health.

investigation to examine for whom these treatments may be most effective.

While baseline variables have not consistently predicted weight loss, early response (ER) to other treatments, at approximately 4–8 weeks, has been shown to consistently predict longer-term weight loss success [4–7]. Early non-response (ENR) may determine the need for additional interventions such as add-on complementary therapies, treatment replacement, or treatment discontinuation [8]. By discontinuing treatment in patients unlikely to benefit, clinicians may reduce exposure to ineffective therapies, improve the benefit–risk ratio for patients, and use health resources more efficiently [4]. Applying an early response approach can therefore be seen as an aid to clinical decision making and more effective use of health care interventions in patients with overweight/obesity.

Studies investigating early response to weight loss treatment have primarily focused on the effects of the treatment itself [4, 9, 10]. However, in studies where all participants receive active treatment, such as studies of medications for weight loss or medications for bronchodilation [11, 12], the early response between treatments has been compared. In the Randomised evaluation of Efficacy and Safety of the Epitomee capsule Trial (RESET), all participants received the same lifestyle intervention to promote dietary modification and physical activity for weight loss, with participants randomly assigned to receive the Epitomee device or a placebo [3].

Therefore, this post hoc analysis of RESET aimed to characterise the early response to treatment and its effect on weight loss at the end of 24 weeks, and to examine whether weight loss differs between the Epitomee and placebo treatments (when both are receiving the same lifestyle intervention) for participants identified as early responders.

## 2 | Materials and Methods

### 2.1 | Study Design

As previously reported, RESET was a prospective, randomised, double-blind, placebo-controlled, adaptive trial conducted at 9 sites in the US. The primary objective of the study was to compare the percentage change from baseline body weight to 24 weeks with the Epitomee capsule versus a visually matching placebo capsule. RESET also examined the proportion of Epitomee-treated participants achieving ≥5% weight loss and compared this with a predefined threshold of 35% achieving this magnitude of weight loss.

The Epitomee capsule is a novel, oral, and a drug-free medical device designed to induce weight loss in participants with overweight and obesity. Composed of superabsorbent polymer particles and a pH sensitive polymer envelope, the Epitomee capsule self-expands in the stomach into an elastic semi-rigid triangular gel structure that resists stomach peristaltic waves and is hypothesized to activate sensory mechanoreceptors in a similar mechanism as food in the stomach to promote early satiety signalling. The Epitomee capsule has a purely mechanical mechanism of action; it maintains mechanical rigidity for hours until envelope disintegration. The Epitomee capsule has no caloric content and no chemical activity. Shortly after reaching the intestine, it disintegrates into small particles naturally excreted through the GI tract [1, 2].

Both the Epitomee and placebo groups were provided a high-intensity lifestyle intervention which included 14 brief (15 min) face-to-face visits, delivered by a registered dietitian or similar health professional [13, 14]. Participants were administered the Epitomee capsule or placebo capsule, twice daily, along with lifestyle counselling for 24 weeks. Participants were instructed to take each capsule with two cups of water (16 oz), approximately 30 min before the two main meals. The schedule of treatment delivery, the lifestyle intervention, and assessments for the RESET study have been described previously [3].

### 2.2 | Participants

The RESET study included adult participants aged ≥18 years with a body mass index (BMI) ranging from 27 to 40 kg/m$^2$ who had either normoglycemia or prediabetes. Participants with normoglycemia were defined as fasting plasma glucose (FPG) <100 mg/dL and haemoglobin A1c (HbA1c) <5.7%. Participants with prediabetes were defined as FPG ≥100 mg/dL and <126 mg/dL and HbA1c ≥5.7% and ≤6.4% and could be untreated or on a stable dose of metformin for at least 4 months.



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A metformin dose of up to 2000 mg/day inclusive was allowed. Participants were required to have previously attempted to lose weight using a medically supervised or self-directed diet but to have no prior use of any gastric medical device and any intent to undergo gastric surgery or banding during the study period or within 6 months of study completion. Participants engaged in a run-in period to demonstrate their ability to ingest placebo-device capsules and to self-monitor their weight, food intake, and physical activity with the accessories provided (WiFi digital weight scale, study mobile app, wearable activity monitor). The full list of inclusion and exclusion criteria can be found at clinicaltrials.gov (NCT04222322).

All participants provided written informed consent prior to performing any study-related activities or evaluations. The study was conducted in accordance with International Council for Harmonisation E6, Guidelines for Good Clinical Practice, ISO 14155:2011, the US Codes of Federal Regulations (21CFR parts 11, 50, 54, 56, 812, and 814), and the Declaration of Helsinki. Study protocols were approved by independent ethics committees or institutional review boards at each study site, and the study protocol was registered on clinicaltrials.gov (NCT04222322).

## 2.3 | Outcome Measures

Weight was measured in duplicate at all study visits by trained assessors, with the participant wearing lightweight clothing with shoes removed. The average of the duplicate measures of weight was used for data analysis. BMI was computed using the baseline height and averaged weight measurements across study visits.

For this post hoc analysis, the early response was defined at >2% weight loss at week 8 of the intervention. This criterion was selected after consideration of several factors including the identification of week 8 as the earliest time point at which the difference between early responders and early non-responders reached statistical significance ($p < 0.05$) (Figure 1) and how the early weight loss response was defined in other studies. Barnes et al. reported that weight loss at week 6 was predictive of weight loss achieved at the end of treatment measured at week 12 and at 3 months of follow-up and 12 months of follow-up [5]. Unick et al. reported that weight loss at week 8 was predictive of weight loss response at 12 months [15]. Therefore, weight loss at week 8 was used to define early response in this post hoc analysis of RESET. Unick et al. used >3% weight loss to define early response; however, the intervention in that study provided meal replacements to study participants and the intervention was implemented across a 12-month period [15]. Therefore, for RESET, which implemented a 24-week intervention, a more conservative ≥2% weight loss was used to define early response.

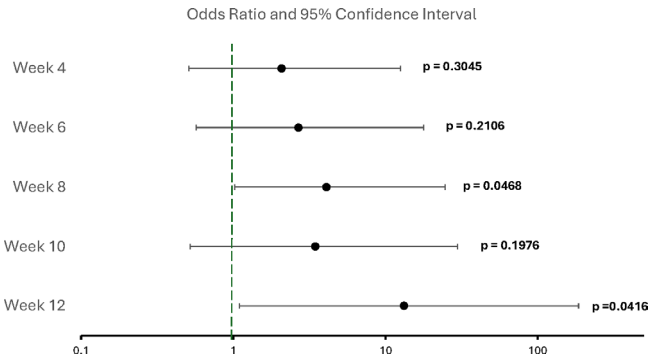


**FIGURE 1** | Likelihood of achieving ≥5% weight loss at week 24 in Epitomee-treated participants: Comparison between early responders and early non-responders.

## 2.4 | Statistics

Statistical analyses were performed using SAS Version 9.4 Windows 2008 Terminal and Python Version 3.9 employing statistical models and Sklearn modules for statistical calculations. Statistical significance was defined as $p < 0.05$.

Descriptive statistics, including mean ± standard deviation for continuous variables and proportions for categorical variables, are reported. The proportion of participants classified as early responders was compared between the Epitomee and placebo groups using the Chi-square test. Comparative post hoc analyses were conducted between Epitomee and placebo early responders assessing percentage change in baseline body weight at week 24. Continuous weight-related variables were analysed using the mixed model for repeated measures (MMRM), following the approach previously reported [3]. The comparison of Epitomee to placebo for the proportion of participants reducing weight by ≥5.0%, ≥7.0%, ≥10.0% or ≥15.0% of baseline body weight at week 24 and the shift in BMI classification from baseline to 24 week were assessed using logistic regression. Safety data, which included incidence, severity and causality of all AEs, were presented as observed proportions and coded according to MedDRA. The analyses presented in this study were conducted on observed data with no imputation and interpolation. Participants with missing data at key observed time points (baseline, week 8) were excluded from the analysis. Participants who dropped out were considered (non-responders at week 24 as they did not achieve ≥5.0% of their baseline body weight).

Analyses were conducted to characterise early weight loss criteria (≥2% weight loss at week 8) with Epitomee or placebo and its association with correctly predicting which participants would achieve >5% weight loss at 24 weeks. For that purpose, we computed the positive predictive value (PPV; i.e., proportion of participants achieving the early response criteria who had >5% weight loss at week 24) and the negative predictive value (NPV; i.e., proportion of participants not achieving the early response criteria who had <5% weight loss at 24 weeks). The percentage of the correctly predicted value was calculated from PPV and NPV as the following:

> (Percentage of Correctly Predicted Value = $((n_{PPV} + n_{NPV})/N)*100$); where n represents the number of participants classified to represent the PPV or NPV, and N represents the total sample of participants.

To provide a clinical reference for other early response weight loss criteria and timepoints, the PPV, NPV, and percent of correctly predicted value were computed for weeks 4, 6 and 8 for >2%, ≥3%, and >4% weight loss (see Tables 2 and S1).



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The Odds Ratio and 95% confidence interval (OR [95% CI]) were computed to examine the likelihood of achieving > 5% weight loss at week 24 for participants classified as meeting the early response criterion (≥ 2% weight loss) compared to early non-responders (< 2% weight loss), with this computed separately for Epitomee and placebo (see Figure 1). Analysis was done using logistic regression with weight loss achieved between weeks 2–12 as dichotomous predictors.

## 3 | Results

Of the 279 individuals who enrolled in the study, 250 (90%) had weight measurements at week 8 (Consort diagram provided in Figure S1). Of these participants, 64.5% (80/124) in Epitomee and 61.9% (78/126) in placebo achieved the criterion to be classified as an early responder, with the proportion of early responders not differing by treatment condition ($p = 0.6706$). Demographic and baseline characteristics of all randomised and early-responder participants are shown in Table 1. Early responders, whether on Epitomee or placebo, were of similar age (Epitomee; 50.3 ± 13.0 years, placebo; 49.7 ± 13.4 years) and similar mean BMI (34.2 ± 3.4 kg/m$^2$ in Epitomee and 33.7 ± 3.1 kg/m$^2$ in the placebo). There was no evident difference in early responder prevalence by BMI category, and the responder prevalence was similar to the BMI class distribution at study entry. Obesity class I early responders were 53.8% and 50.0% in the Epitomee and placebo groups, respectively, or class II (33.8% and 37.2% of the Epitomee and placebo participants, respectively).

### 3.1 | Predictive Value of Early Responder Classification

For the participants in Epitomee, classification as an early responder had a PPV of 76.2%, whereas classification as an early

**TABLE 1** | Baseline demographics and clinical characteristics for all participants and early responders (≥ 2% weight loss at 8 week) by treatment.

| | Epitomee treatment | | Placebo treatment | |
|---|---|---|---|---|
| | All randomised $N = 138$ | Early responders[d] $N = 80$ | All randomised $N = 141$ | Early responders[d] $N = 78$ |
| Age (years)[a] | 48.5 ± 12.5 | 50.3 ± 13.0 | 48.6 ± 12.4 | 49.7 ± 13.4 |
| Gender[b] | | | | |
| Female | 80.4% (111) | 76.2% (61) | 79.4% (112) | 74.4% (58) |
| Male | 19.6% (27) | 23.8% (19) | 20.6% (29) | 25.6% (20) |
| Race/Ethnicity[b] | | | | |
| White | 73.2% (101) | 82.5% (66) | 69.5% (98) | 71.8% (56) |
| Black or African-American | 21.0% (29) | 10.0% (8) | 25.5% (36) | 17.9% (14) |
| Other/unknown | 5.8% (8) | 7.5% (6) | 5.0% (7) | 10.3% (8) |
| Weight (kg)[a] | 95.9 ± 15.4 | 97.9 ± 16.0 | 95.7 ± 15.4 | 95.8 ± 14.6 |
| Height (cm)[a] | 167.3 ± 9.1 | 168.7 ± 9.2 | 168.2 ± 8.7 | 168.4 ± 8.9 |
| BMI by BMI entry category, (kg/m$^2$) | 34.1 ± 3.3 | 34.2 ± 3.4 | 33.7 ± 3.4 | 33.7 ± 3.1 |
| Overweight (kg/m$^2$) | 28.5 ± 0.9 (13) | 28.1 ± 1.0 | 28.5 ± 0.7 (23) | 28.8 ± 0.8 |
| Obesity Class I (kg/m$^2$) | 32.4 ± 1.6 (66) | 32.4 ± 1.6 | 32.6 ± 1.3 (63) | 32.5 ± 1.4 |
| Obesity Class II (kg/m$^2$) | 37.0 ± 1.4 (54) | 37.2 ± 1.3 | 37.1 ± 1.4 (54) | 36.9 ± 1.4 |
| Obesity Class III (kg/m$^2$)[a,c] | 40.4 ± 0.5 (5) | 40.4 ± 0.5 | 40.0 (1) | — |
| Waist Circumference (cm)[a] | 106.7 ± 11.1 | 109.2 ± 10.6 | 107.6 ± 11.7 | 107.3 ± 10.7 |
| Proportion in BMI Categories[b] | | | | |
| Overweight | 9.4% (13) | 6.2% (5) | 16.3% (23) | 12.8% (10) |
| Obesity Class I | 47.8% (66) | 53.8% (43) | 44.7% (63) | 50.0% (39) |
| Obesity Class II | 39.1% (54) | 33.8% (27) | 38.3% (54) | 37.2% (29) |
| Obesity Class III | 3.6% (5) | 6.2% (5) | 0.7% (1) | 0.0% (0) |

[a]Mean ± standard deviation.
[b]% (*n*).
[c]4 ineligible participants with diabetes included by mistake. Study's medical monitor and the responsible principal investigators (PIs) decided to allow their continued participation.
[d]No significant differences between the Epitomee early responders and the placebo early responders.



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**TABLE 2** | Positive and negative predictive values for achieving at least 5% weight loss at week 24 with Epitomee using different early response criteria.

| Week | Early response criterion (%) | N[a] | Early responders | | | Early non-responders | | | Correctly predicted value of ≥5% weight loss (%) |
|---|---|---|---|---|---|---|---|---|---|
| | | | Early response *n* (%) | Mean week 24 weight loss (%) in early responders | Positive predictive value ≥5% at 24 weeks, *n* (%)[b] | Early nonresponse, *n* (%) | Mean week 24 weight Loss (%) in early nonresponders | Negative predictive value ≥5% at 24 weeks, *n* (%)[b] | |
| 4 | ≥2 | 131 | 72 (55.0) | −9.8 | 56 (77.8) | 59 (45.0) | −1.5 | 52 (88.1) | 82.4 |
| | ≥3 | 131 | 53 (40.5) | −11.2 | 47 (88.7) | 78 (59.5) | −2.4 | 62 (79.5) | 83.2 |
| | ≥4 | 131 | 26 (19.8) | −12.6 | 24 (92.3) | 105 (80.2) | −4.7 | 66 (62.9) | 68.7 |
| 6 | ≥2 | 127 | 83 (65.4) | −8.9 | 60 (72.3) | 44 (34.6) | −1.0 | 41 (93.2) | 79.5 |
| | ≥3 | 127 | 63 (49.6) | −10.6 | 52 (82.5) | 64 (50.4) | −2.1 | 53 (82.8) | 82.7 |
| | ≥4 | 127 | 49 (38.6) | −11.7 | 43 (87.8) | 78 (61.4) | −2.8 | 58 (74.4) | 79.5 |
| 8 | ≥2 | 124 | 80 (64.5) | −9.3 | 61 (76.2) | 44 (35.5) | −0.8 | 42 (95.5) | 83.1 |
| | ≥3 | 124 | 68 (54.8) | −10.6 | 58 (85.3) | 56 (45.2) | −1.1 | 51 (91.1) | 87.9 |
| | ≥4 | 124 | 56 (45.2) | −11.4 | 51 (91.1) | 68 (54.8) | −2.2 | 56 (82.4) | 86.3 |

[a]The analysis is based on ITT who have available data for the responder criteria week.
[b]Positive predictive value is defined as the percentage of early responders who were week 24 responders (successfully lost at least 5% of baseline weight at week 24).

non-responder had a NPV of 95.5% (Table 2). By comparison, for placebo, classification as an early responder had a PPV of 61.5%, whereas classification as an early non-responder had a NPV of 91.7% (Table S1). The Odds Ratios for the likelihood of success (achieve ≥5% weight loss at week 24) in early responders versus early non-responders in participants receiving Epitomee was 4.10 (95% CI: 1.02, 16.46) and in participants receiving placebo was 2.38 (95% CI: 0.62, 9.21) (Figure 1).

### 3.2 | 24 Week Weight Loss Based on Early Responder Classification

Average weight loss at 24 weeks was significantly greater in Epitomee early responders compared to early non-responders (−9.3% ± 6.0% vs. −0.8% ± 2.9%; $p < 0.0001$; Table 2). A similar response was observed for placebo, with early responders achieving greater weight loss at 24 weeks compared to early non-responders (−6.9% ± 4.3% vs. −1.0% ± 3.0%; $p < 0.0001$; Table S1). Moreover, Epitomee early responders had a significantly greater weight loss at 24 weeks than placebo early responders (−9.3% [95% CI: −10.6, −7.9] vs. −6.9% [95% CI: −7.9, −6.0]; difference = 2.3% [95% CI: 0.7, 4.0], $p < 0.0001$; Figure 2A).

The proportion of early responders achieving weight loss at 24 weeks of >5%, ≥%, ≥10%, and ≥15% in participants receiving Epitomee or placebo is shown in Figure 2B. The proportion of early responders receiving Epitomee who achieved ≥5%, ≥7%, and ≥10% weight loss at week 24 was significantly greater than early responders receiving placebo ($p = 0.0472$, $p = 0.0045$, $p = 0.0025$, respectively). The proportion of participants achieving ≥15% weight loss at 24 weeks did not differ between Epitomee and placebo.

Early responders subgroup analysis per BMI categories showed that regardless of baseline BMI category, participants treated with Epitomee experienced greater weight loss compared to placebo in overweight, obesity I, and obesity II [Overweight: −11.1% ± 1.8% and −7.3% ± 4.9%, respectively, $p < 0.0052$; Obesity I: −8.9% ± 5.5% and −6.8% ± 4.1%, respectively, $p < 0.0003$; Obesity II: −9.4% ± 7.3% and −7.0% ± 4.3%, respectively, $p < 0.0016$] (Figure 3A–C). Also, significantly more Epitomee early responders improved their BMI classification category ($p = 0.0150$), and although not statistically significant, more of the Epitomee early responders shifted to normal BMI (BMI < 25 kg/m$^2$) (Figure 3D).

### 3.3 | Adverse Events

Adverse events in the study population as a whole have been described [3]. We further analyse adverse events among early responders. The greater improvements observed in Epitomee early responders with ≥2% weight loss at week 8, compared with placebo early responders, were generally not accompanied by an increase in AEs. The safety profile was similar between the groups, regardless of treatment assignment (Table 3), with overall AEs incidence of 87.5% in the Epitomee early responders and 85.9% in the placebo early responders, and GI-related AEs of 37.5% in the Epitomee early responders and 39.7% in the placebo early responders. There were no significant differences between



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the Epitomee early responders and the placebo early responders in any of the presented parameters.

## 4 | Discussion

This study demonstrates that early response to treatment (≥2% weight loss at week 8) was associated with greater odds of achieving clinically significant weight loss of at least 5% at week 24 compared to early non-response, with the Odds Ratio being 4.10 (95% CI: 1.02, 16.46) for Epitomee and 2.38 (95% CI: 0.62, 9.21) for placebo; Figure 1. Despite no significant difference by treatment assignment in the proportion of participants meeting the weight loss criteria to be classified as an early responder (64.5% vs. 61.9%, in the Epitomee and placebo, respectively), early responders to Epitomee had a significantly greater weight loss at week 24 than placebo early responders (9.3% vs. 6.9%, Figure 2, Panel A). Significantly greater weight loss was observed in early responders receiving Epitomee compared to early responders to placebo regardless of baseline BMI category (overweight, obesity class I and class II) (Figure 3, Panels A–C). The primary findings for RESET showed that weight loss was significantly greater with Epitomee compared to placebo (−6.6% ± 6.5% vs. −4.6% ± 4.7%) [3], and these post hoc analyses support that the pattern favouring Epitomee over placebo remains for participants who were an early responder to either treatment.

This study also showed that the early response to Epitomee, compared to placebo, was more consistently predictive of achieving ≥5% weight loss at week 24. With Epitomee, early responders, compared to non-responders, were 4.10 times more likely to achieve >5% weight loss at week 24, whereas with placebo early responders, compared to non-responders, were 2.38 times more likely to achieve this magnitude of weight loss. In the Look AHEAD study, failure to achieve a 2% weight loss at 1 month or 3% weight loss at 2 months significantly increased the likelihood of *not* achieving a clinically significant weight loss at Year 1. For example, participants failing to achieve a ≥2% weight loss at Month 1 with lifestyle intervention were 4.8 times and 5.6 times more likely to also not achieve a ≥5% and a ≥10% weight loss at Year 1, respectively, compared to those losing ≥2% initially. These odds were 8.4 and 11.6 times greater respectively, when using a 3% weight loss threshold at Month 2 [8].

Weight loss of ≥5% is clinically meaningful. The Look AHEAD trial demonstrated that improvements in systolic and diastolic blood pressure, HDL cholesterol, and triglycerides began with a weight loss of at least 5% [16]. Other studies have also shown clinically relevant improvements in CVD risk factors, with a 5%–7% reduction in baseline body weight [17–21]. However, additional health benefits may be realised at even higher levels of weight loss. The Diabetes Prevention Program study showed that weight loss of more than 7% was clinically meaningful and was able to prevent the progression from prediabetes to diabetes in 67% of participants with impaired glucose tolerance [22]. Moreover, in the Look AHEAD study, an observational analysis of the randomised trial data revealed that achieving ≥10% weight loss in the first year was associated with an approximate 20% reduced CVD risk [23]. Therefore, treatments that enable more patients to achieve this level of weight loss may be

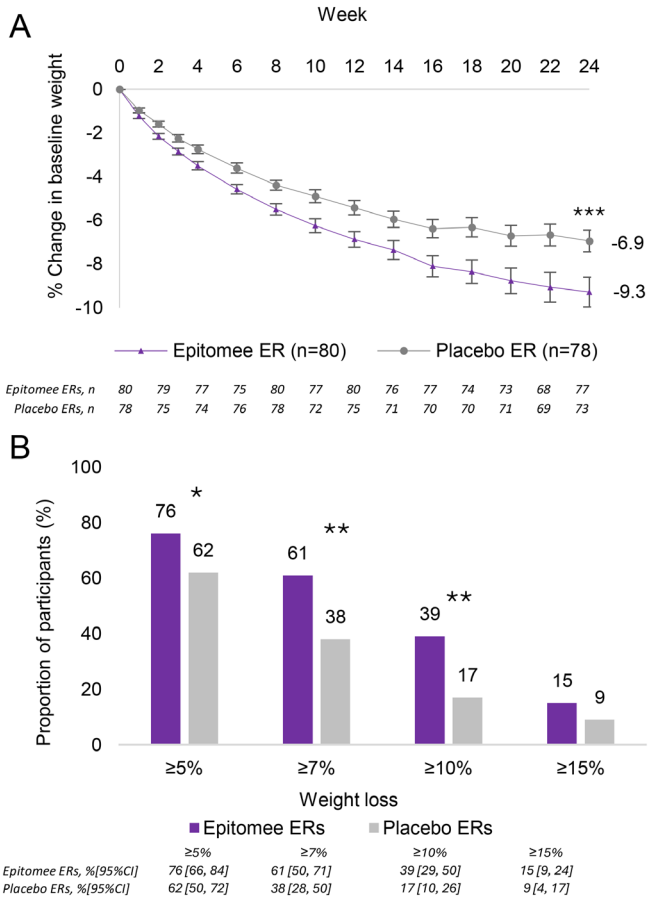


**FIGURE 2** | Weight loss in early responders. (A) Change in early responder's body weight from baseline by week 24. (B) The proportions of early responders achieving ≥5%, ≥7%, ≥10%, and ≥15% weight loss at week 24.

clinically important for diabetes prevention and reduced CVD risk outcomes. In these post hoc analyses of RESET, early response to Epitomee was associated with a greater proportion of participants achieving the clinically meaningful weight loss amounts of ≥5%, ≥7%, and ≥10% (Figure 2, Panel B). While unable to be determined in this study, this pattern of findings may have implications for improving cardiovascular and diabetes risk factors, which will need confirmation in longer-term studies of Epitomee.

Identifying an early response to weight loss may assist clinicians in determining whether to continue treatment, provide additional adjunctive treatment, or pivot to a different treatment to enhance weight loss for the treatment of overweight/obesity. The computed PPV and NPV may be a useful tool for clinicians to consider when examining early response as a predictor of achieving or not achieving ≥5% weight loss by 24 weeks. In this study we presented the PPV and NPV for an early response of ≥2% weight loss at week 8. However, a clinician may want to consider an alternative magnitude of weight loss or at a period other than week 8 when evaluating whether a treatment is likely to result in ≥5% weight loss by 24 weeks. Therefore, we present additional PPV and NPV values for 2%, 3%, and 4% weight loss that are achieved at 4, 6, and 8 weeks of treatment in Tables 2 and S1 as a clinical tool for clinicians.



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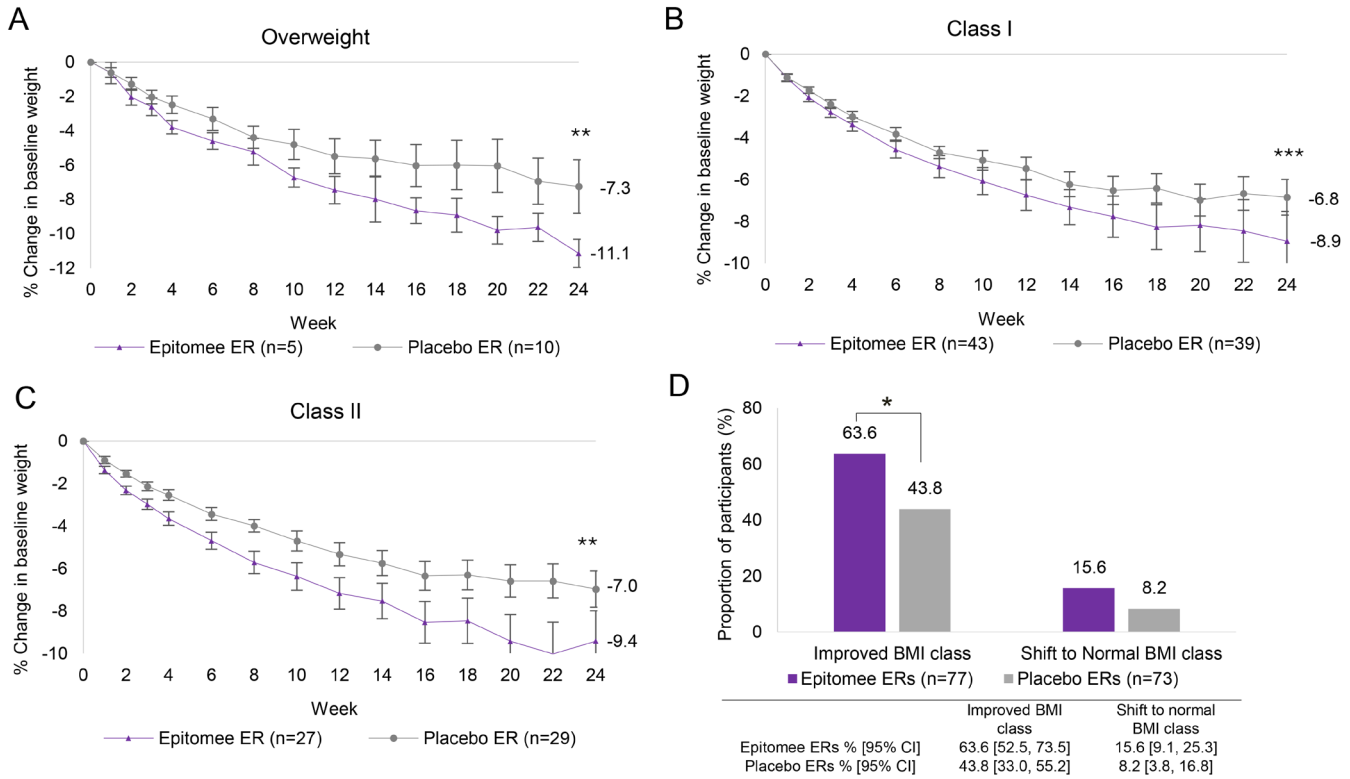


**FIGURE 3** | Weight loss within BMI classification in early responders. (A–C) Improvement in BMI classification category (overweight, class I and class II) from baseline to week 24. (D) Improvement in BMI class and shift to normal BMI class (BMI < 25) from baseline to week 24.

**TABLE 3** | Adverse events in the overall RESET trial and in early responders.

| | Epitomee treatment | | | | Placebo treatment | | | |
|---|---|---|---|---|---|---|---|---|
| | All randomised ($n = 138$) | | Early responders ($n = 80$)[a] | | All randomised ($n = 141$) | | Early responders ($n = 78$)[a] | |
| | Number events | Number of subjects (%) | Number events | Number of subjects (%) | Number events | Number of subjects (%) | Number events | Number of subjects (%) |
| Adverse events | 357 | 119 (86.2) | 219 | 70 (87.5) | 368 | 119 (84.4) | 197 | 67 (85.9) |
| Severe adverse events | 16 | 12 (8.7) | 11 | 8 (10.4) | 18 | 11 (7.8) | 12 | 7 (9.6) |
| GI related | 83 | 54 (39.1) | 51 | 30 (37.5) | 98 | 58 (40.4) | 51 | 31 (39.7) |
| Serious adverse events | 1 | 1 (0.7) | 1 | 1 (1.3) | 1 | 1 (0.7) | 1 | 1 (1.4) |
| PI assessment for device related SAE | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) |

[a]There were no significant differences between the Epitomee early responders and the placebo early responders in any of the presented parameters.

### 4.1 | Strength and Limitations

A key strength of this study was the comparison between early responders in the Epitomee group with early responders in the placebo group. Identification of a subset of early responders in both treatments provides an early opportunity to consider whether a participant may be likely to achieve 5% or more weight loss by 24 weeks. The study, however, included only 24 weeks of treatment, which limits our knowledge of longer-term weight loss and weight-loss maintenance and possible health benefits. Moreover, the analyses presented are post hoc and not part of an a priori statistical plan, and therefore findings should be interpreted with caution.

The Epitomee capsule also requires water consumption when taken prior to a meal. Both the Epitomee and placebo groups were instructed to consume water when taking their assigned capsule prior to a meal. It has been shown that water consumption prior to a meal while also consuming a hypocaloric diet may contribute to modest additional weight loss compared to



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a hypocaloric diet alone [24]. However, future studies of the Epitomee capsule may benefit from closer monitoring of the amount of water consumed to understand whether this is contributing to the variability in weight loss while also recognising the importance of hydration for health benefits beyond weight reduction.

## 4.2 | Conclusion

Early response at 8 weeks predicts clinically meaningful weight loss at 24 weeks in adults with overweight or obesity and was observed in 64.5% of Epitomee participants. Weight loss at week 24 was greater in ER to Epitomee compared to placebo ($-9.3\% \pm 6.0\%$ vs. $-6.9\% \pm 4.3\%$; $p < 0.0001$). Additionally, early responders to Epitomee achieved greater weight loss at week 24 and were more likely to achieve 5%, 7%, and 10% weight loss at 24 weeks versus early responders receiving placebo. This may support that early response to the Epitomee capsule can be predictive of clinically meaningful weight loss that has been associated with improving health outcomes. Moreover, clinicians should monitor early response to treatment and provide adjunctive treatments or possibly pivot to an alternative treatment when an early response is not observed. This may inform how clinicians consider early response to non-pharmacotherapy treatment to enhance weight loss, which may result in an enhanced health-risk profile in adults with overweight or obesity.

### Author Contributions

John M. Jakicic contributed to the investigation, writing the original draft, and reviewing and editing the draft. Donna H. Ryan contributed to the conceptualisation, writing the original draft, and reviewing and editing the draft. Jamy D. Ard contributed to the investigation 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 conceptualisation, methodology, investigation, and reviewing and editing of the draft. Holly R. Wyatt contributed to the investigation and reviewing and editing of the draft. Harold E. Bays contributed to the investigation as well as reviewing and editing the draft. Frank L. Greenway contributed to the investigation and reviewing and editing the draft. Sharon Leonard contributed to the supervision of the study and to reviewing and editing the draft. Yael Kenan contributed to the conceptualisation, methodology, investigation, data curation, reviewing and editing the draft, visualisation, supervision, and project administration. Eti Ganon-Elazar contributed to the investigation, data curation, reviewing and editing the draft, visualisation, and data administration. Thomas A. Wadden contributed to the investigation, resources, and reviewing and editing of the draft.

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### Conflicts of Interest

John M. Jakicic has received grant support from Epitomee Medical Ltd. and the National Institutes of Health, consulting fees from the Scientific Advisory Committee for Wondr Health Inc., and holds a volunteer leadership position at the American College of Sports Medicine. Jamy D. Ard has received grant support from Nestle Healthcare Nutrition, Eli Lilly, Boehringer Ingelheim, Epitomee Inc., UnitedHealth Group R&D, KVKTech, and WW, consulting fees from Nestle Healthcare Nutrition, Eli Lilly, Optum Labs R&D, Novo Nordisk, Intuitive, Regeneron, Brightseed, Level2, WW, Amgen, and Boehringer Ingelheim, receipt of equipment, materials, drugs, medical writing, gifts or other services from KVKTech, WW, and Nestle 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, Amgen, Astra Zeneca, Biohaven, Boehringer Ingelheim, Calibrate, Carmot/Roche, CinRx, Currax, Epitomee, Fractyl, Gila, Lilly, Nestle, Novo Nordisk, Scientific Intake, Structure Therapeutics, Wondr Health, and Zealand, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Novo Nordisk and Lilly, participated on a data safety monitoring board or advisory board for Lilly, Rhythm, and Cin Rx, and holds stock options for Epitomee, Calibrate, Roman, Scientific Intake, and Xeno. Patrick M. O'Neil has received grant support from Epitomee Medical Ltd., Novo Nordisk, and Eli Lilly, consulting fees from Novo Nordisk, participated on an advisory board for Novo Nordisk, and has an unpaid leadership or fiduciary role for the Diabetes Initiative of South Carolina. Robert F. Kushner has received grant support from Epitomee Medical Ltd., participated on a data safety monitoring board or advisory board for Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Structure, Altimmune, Regeneron, Weight Watchers, and Currax, and holds a leadership or fiduciary role on the American Board of Obesity Medicine. Holly R. Wyatt has received grant support from Epitomee Medical Ltd., General Mills, Novo Nordisk, Gelesis, and the National Cattlemen's Beef Association, royalties or licences from State of Slim (book), IP owned by Shakabuku, and IP licensed to the University of Colorado, consulting fees from Gelesis, honoraria from the Cardio Metabolic Health Conference and the Institute for Medical and Nursing Education, holds a patient 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 Health. Harold E. Bays has received grant support from 89Bio, Alon Medtech/Epitomee, Altimmune, Amgen, Bioage, Boehringer Ingelheim, Carmot, Chorus/Bioage, Eli Lilly, Evidera, Kallyope, Novartis, NovoNordisk, Pfizer, Regeneron, Satsuma, Selecta, Shionogi, Skye/Birdrock, Veru, Viking, and Vivus; consulting fees from 89Bio, Altimmune, Amgen, Boehringer Ingelheim, Kiniksa, HighTide, Lilly, Novo Nordisk, Regeneron, Veru, Zomagen, and ZyVersa; participated on an advisory board for Epitomee, Altimmune, Novo Nordisk, Boehringer Ingelheim, and Kiniksa; and serves as Chief Science Officer and President-Elect of The Obesity Medicine Association. Frank L. Greenway has received grant support from Epitomee Medical Ltd., consulting fees from Altimmune, DexCom, Basic Research, and NovMeta Pharma, support for meeting attendance from BioHaven, holds patents issued or pending (US 11534442, US 11058662, US 10897921, US 10507194, US 9999601, US 8334000, US 7709031, US 17/245538, and US 15/565367), and stock or stock options from Pep—19, Slim Health Nutrition, Rejuvenate Bio, Energesis, Ketogenic Health System, GATC Health, and Uplifting Results Inc. Sharon Leonard has received grant support from Epitomee Medical and Eli Lilly Pharmaceuticals, consulting fees from Epitomee Inc. and Eli Lilly Pharmaceuticals, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Epitomee Inc. and Eli Lilly Pharmaceuticals, and support for attending meetings and/or travel from Epitomee Inc. and Eli Lilly Pharmaceuticals. Yael Kenan is an employee of Epitomee Medical Ltd. and holds stock or stock options. Eti Ganon-Elazar is an employee of Epitomee 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, Epitomee Medical, and Novo Nordisk, and has served on scientific advisory boards for Eli Lilly, Novo Nordisk, and WW.

### Data Availability Statement

Research data are not shared.



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