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Weight and cardiometabolic effects of a novel oral shape-shifting superabsorbent hydrogel capsule: Prespecified and exploratory analysis of the Epitomee capsule RESET study

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ABSTRACT

Background: Management of obesity potentially improves cardiometabolic risk factors in patients with metabolic syndrome (MetS). The Epitomee capsule is a non-pharmacological, biodegradable device treatment for weight reduction in patients with overweight and obesity.

Methods: This secondary analysis of the Randomized Evaluation of Safety and Efficacy of the Epitomee capsule Trial (RESET) (a randomized, 24-week, multicenter, placebo-controlled, double-blind trial that enrolled 279 adults aged ≥18 years with a BMI of 27–40 kg/m2) evaluated changes in cardiometabolic parameters in participants treated with Epitomee or placebo combined with lifestyle counseling among (a) the entire RESET study population, and (b) participants meeting diagnostic criteria for prediabetes. Predefined and exploratory endpoints included changes in waist circumference, glycemic parameters, blood pressure, and lipid blood levels; this analysis also assessed percent weight loss in participants with MetS.

Results: Waist circumference, systolic and diastolic blood pressure and some measures of glycemia and lipids, improved with both Epitomee and placebo with no significant differences. Participants with prediabetes treated with Epitomee showed significantly greater reductions in HOMA-IR ($p < 0.007$) and insulin levels ($p < 0.003$) than the placebo group. Participants with MetS at baseline experienced significantly greater percent change in initial weight when treated with the Epitomee capsule ($n = 27$) compared to placebo ($n = 31$), −8.3% vs −5.2 %, respectively ($p < 0.0004$). Similar percentages of participants with MetS in both groups achieved ≥5 % weight reduction (59.3 % and 54.8 %, in Epitomee and placebo groups respectively). Significantly more participants with MetS treated with Epitomee achieved ≥10 % weight reduction compared with those treated with placebo (40.7 % vs. 6.5 %, respectively, $p < 0.002$).

Conclusion: Treatment with either Epitomee and placebo combined with lifestyle improve cardiometabolic risk factors. Compared to placebo, Epitomee significantly reduced HOMA-IR and insulin levels in participants with

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prediabetes. Among participants with MetS, Epitomee significantly reduced body weight [ClinicalTrials.gov ID NCT04222322].

1. Background

Overweight and obesity contribute to chronic diseases such as diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease (CVD) and cancer [1] and obesity ranks as the fourth leading cause of death globally [2]. Metabolic syndrome (MetS) is a cluster of risk factors associated with an increased risk of CVD. MetS prevalence is increasing across all age groups [3]. MetS is characterized by abdominal obesity, hyperglycemia, hypertension, and dyslipidemia [4]. Weight reduction among patients with obesity often requires a multifactorial and multidisciplinary approach, such as via healthful nutrition, physical activity, behavior modification (i.e., lifestyle intervention), pharmacotherapy, and surgical interventions.

The Epitomee capsule is an FDA approved, novel, orally self-administered device, designed to induce weight reduction in participants with overweight and obesity. Composed of pharmaceutical grade polymers and bonding materials, the Epitomee capsule self-expands in the stomach into a pH-sensitive gel structure, combining superabsorbent polymer miniature particles capable of absorbing water (up to 100 times their dry weight) and decreasing in volume with rising ion concentration, along with a pH-sensitive polymer envelope stable up to pH of 6.5. Upon ingestion and water absorption, the gel particles expand, forming an elastic triangular structure that resists stomach peristaltic waves, promoting early satiety signaling. Constituted of 97 % water and 3 % polymers, the Epitomee capsule maintains mechanical rigidity for hours until envelope disintegration, with no caloric content and no chemical activity. Within 30 min after reaching the intestine, it disintegrates into small particles that are excreted through the GI tract [5,6].

In the Randomized evaluation of Efficacy and Safety of the Epitomee capsule Trial (RESET), participants treated with the Epitomee capsule for 24 weeks achieved a mean percentage reduction in baseline body weight of 6.6 % [6.5] (mean [standard deviation, SD]), compared with a statistically significantly smaller 4.6 % [4.7] for the placebo group, with both groups treated with an intensive lifestyle program ($P < 0.0001$) [7]. In a prior 12-week single-arm study, weight reduction with the Epitomee capsule correlated with early satiety, decreased snacking, and reduced meal size, and was accompanied by improvements in cardiometabolic risk factors, including waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), and triglyceride (TG) levels [5,6]. The present report describes the results of predefined secondary and exploratory analyses of Epitomee versus placebo regarding cardiometabolic effects of (a) the entire RESET study population, and (b) participants meeting diagnostic criteria for prediabetes. Additionally, percent weight loss was assessed in participants meeting diagnostic criteria for MetS.

2. Methods

2.1. Study design

RESET [7] was a prospective, randomized, double-blind, placebo controlled, multi-center, study conducted in the US between 2020 and 2023. Participants were administered Epitomee or placebo capsule, taken twice daily, along with intensive lifestyle consultation for 24 weeks. Lifestyle consultation included 14 brief (15 min) face-to-face visits, delivered by a registered dietitian or similar health professional [8,9]. Each Epitomee capsule was self-administered with two cups of water, approximately 30 min before the two main meals. At each visit, the participants' weight and vital signs were recorded.

The study was conducted in accordance with International Council for Harmonization 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. Written approval was obtained from the appropriate institutional review boards at each site prior to site activation. A signed informed consent form was obtained from participants prior to performing any study-related activities or evaluations.

2.2. Patients

Key inclusion criteria for the RESET study included adult participants aged ≥18 years with a body mass index (BMI) ranging from 27 to 40 kg/m2, with either normoglycemia or prediabetes. Normoglycemia was defined as fasting plasma glucose (FPG) < 100 mg/dL and hemoglobin A1C (HbA1c) < 5.7 %. Prediabetes was defined as one or more of the following.

- Fasting Plasma Glucose (FPG): A fasting blood sugar level from 100 to 125 mg/dL (5.6–6.9 mmol/L) inclusive.
- Glycated Hemoglobin (A1C): An A1C level from 5.7 % to 6.4 % (39–46 mmol/mol) inclusive.

For the full list of inclusion and exclusion criteria, please refer to ClinicalTrials.gov ID NCT04222322.

2.3. Efficacy evaluation

Components of the MetS were prespecified secondary endpoints and included waist circumference, FPG, systolic/diastolic blood pressure (SBP/DBP), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), each assessed from baseline (randomization visit) to week 24. Change in SBP and DBP were also assessed in participants with BP ≥ 120/80mmHg at baseline [10]. Additional prespecified metabolic secondary endpoints included fasting serum insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR), and HbA1c. In addition, exploratory analysis assessing changes from baseline in glycemic parameters was performed on participants with prediabetes at baseline.

Exploratory analyses on participants meeting the diagnostic criteria for MetS at baseline included percent change from baseline in body weight and changes in the proportion of study participants meeting the diagnostic criteria for MetS at follow up. The metabolic syndrome was defined as [11] study participants with 3 or more of the following:

- o Elevated waist circumference [males ≥40 inches (102 cm); females ≥35 inches (88 cm)] or Asian males ≥90 cm; Asian females ≥80 cm) [8] measured as the distance between the inferior border of the rib cage and the superior aspect of the iliac crest
- o Elevated fasting glucose ≥100 mg/dL (5.6 mmol/L) or use of medication for type 2 diabetes mellitus
- o Elevated blood pressure (≥130/85 mm Hg or use of medication for hypertension)
- o Elevated triglycerides ≥150 mg/dL (1.7 mmol/L), or use of medications for high triglycerides
- o Reduced HDL-C: males <40 mg/dL (1.03 mmol/L); females <50 mg/dL (1.29 mmol/L), or use of medications for low HDL-C

The full list of prespecified and exploratory endpoints is included in Supplement Table S1. Analysis of safety of the Epitomee capsule vs. placebo was previously presented [7]. That analysis showed a safety profile of the Epitomee capsule comparable to that of the placebo.

2.4. Statistics

Mean changes from baseline, in weight, waist circumference, diastolic and systolic blood pressure and Lab values (as specified above) were assessed for both the Epitomee and the placebo treatment groups. Between and within groups analyses utilized mixed models for repeated measures (MMRMs).

The proportion of weight reduction was analyzed through logistic regression. The proportions of participants reversing to normal levels of lab values are displayed and were analyzed using chi-square. Abnormality was defined as FPG≥100 mg/dL, Insulin >24.9 uIU/mL, HOMA-IR>1.9, HBA1C ≥ 5.7 %, HDL-C<60 mg/dL and TG ≥ 150 mg/dL. The Wilcoxon rank test was used to analyze FPG, insulin and HOMA-IR in participants with prediabetes completing the study, as the assumption of normality was not met. No imputations or interpolation were applied on missing values. Statistical analysis was performed using Excel and SAS® Version 9.4 Windows® 2008 Terminal, and graphical software was done with Adobe Photoshop 2024. A p-value <0.05 was considered statistically significant.

3. Results

Of the 279 individuals who enrolled in the study, 240 (86%) completed the 24-week follow-up (i.e., 119 and 121 in the Epitomee and placebo groups, respectively). A consort diagram has been published previously [7] and is provided in Supplemental Fig. S1. Baseline characteristics and demographics were previously described [7]. Overall, the groups were evenly matched across all baseline parameters such as age, gender, weight and ethnicity. Baseline demographics and clinical characteristics are provided in Supplemental Table S2.

3.1. Analysis of the overall RESET population

Waist circumference: In the overall RESET study population, participants treated with Epitomee showed numerically greater reduction in average waist circumference compared to those treated with placebo, but the difference between groups did not reach statistical significance (6.0 ± 7.0 cm vs. 5.0 ± 5.7 cm) (Fig. 1). Both the Epitomee capsule and placebo groups experienced significant reduction in waist circumference from baseline to week 24 ($p < 0.0001$).

Blood Pressure: Participants treated with both Epitomee and placebo in the overall study population and those with elevated BP ≥ 120/80mmHg experienced significant reductions in SBP and DBP from baseline to week 24, with the difference between the groups not being statistically significant (Fig. 2).

Laboratory values: Overall no significant differences were observed between groups in the lab parameters examined in this study (Table 1).

The improvements observed in participants shifted from abnormal to normal levels are presented in Table 1. For example, 68.8 % of participants with increased insulin levels (>24.9 uIU/mL) at baseline in the Epitomee treatment group transitioned to normal levels (≤24.9 uIU/mL). This subgroup experienced a reduction in mean insulin levels of −21.5 ± 11.1 uIU/mL. Participants in both the Epitomee and the placebo groups shifted from abnormal baseline levels to normal levels in the different glycemic and lipid parameters (HbA1C: 38.5 % vs 18.9 %; insulin: 68.8 % vs 42.9 %; TG: 57.9 % vs 47.1 %; HDL-C: 16.4 % vs 12.0 %; FPG: 50 % vs 52 %; HOMA-IR: 29.8 % vs 28.8 %, respectively) (Table 1).

3.2. Analysis of participants with prediabetes

For participants with prediabetes, HOMA-IR, insulin, FPG and HbA1C percent change from baseline after 24 weeks of treatment are presented in Fig. 3. HOMA-IR and insulin percent change from baseline in week 24 was significantly greater for participants with prediabetes

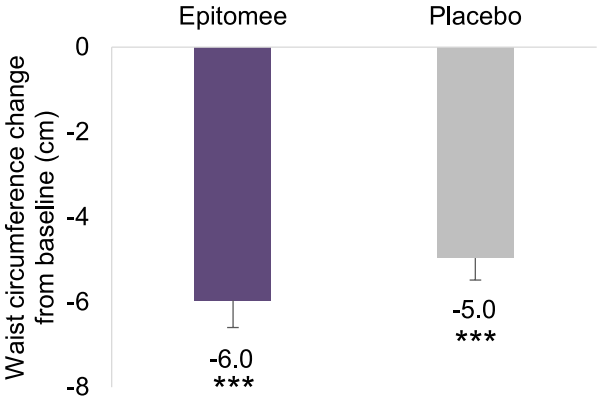

Fig. 1. Change from baseline in waist circumference. No significant difference between the groups was observed. Significant reduction in mean waist circumference from baseline to week 24 was observed in both Epitomee and placebo groups (***$p < 0.0001$).

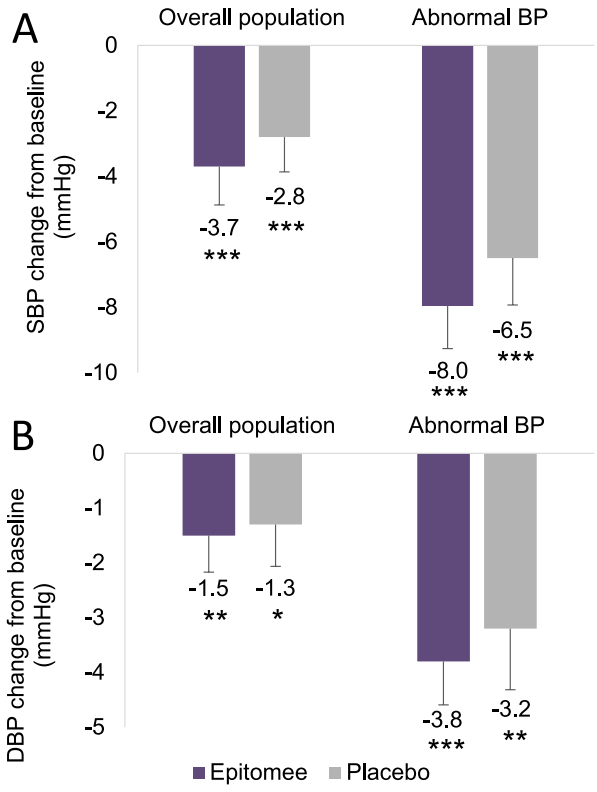

Fig. 2. Change from baseline in Systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the overall population and in those with ≥120/80 mmHg BP at baseline. (A) No significant differences between the groups were observed. Significant reduction in SBP from baseline to week 24 was observed in both Epitomee and placebo groups in the overall population (n = 119, n = 121, respectively) and in participants with ≥120/80 mmHg BP at baseline (n = 77, n = 71, respectively). (B) No significant differences between the groups were observed. Significant reduction in DBP from baseline to week 24 was observed in both Epitomee and placebo groups in the overall population (n = 119, n = 121, respectively) and in participants with ≥120/80 mmHg BP at baseline (n = 77, n = 71, respectively). *$p < 0.05$; **$p < 0.01$; ***$p < 0.0001$.

Table 1
Change from baseline in lab associated risk factors.

	Epitomee capsule				Placebo capsule			
	Baseline Mean ± SD (N)	Week 24 Mean ± SD (N)	Change from baseline Mean ± SD (CI)	Mean ± SD [% (N)] in those who normalized[b]	Baseline Mean ± SD (N)	Week 24 Mean ± SD (N)	Change from baseline Mean ± SD (CI)	Mean ± SD [% (N)] in those who normalized[b]
FPG (mg/dL)	91.3 ± 10.8 (136)	88.6 ± 11.4 (115)	−2.4 ± 10.3 (−4.3, −0.4)[a]	−20.0 ± 12.1[a] [50.0 (10)]	91.4 ± 10.0 (141)	90.3 ± 10.1 (117)	−0.9 ± 10.3 (−2.8,0.9)[a]	−16.1 ± 8.2[a] [52.0 (11)]
Insulin (uIU/mL)	15.9 ± 10.8 (136)	12.9 ± 12.7 (117)	−3.3 ± 13.1 (−5.7, −0.9)[a]	−21.5 ± 11.1[a] [68.8 (11)]	13.8 ± 9.1 (141)	11.5 ± 7.6 (119)	−1.3 ± 5.9 (−2.4, −0.3)[a]	−8.8 ± 3.0[a] [42.9 (3)]
HOMA-IR	3.8 ± 2.9 (136)	3.0 ± 3.4 (115)	−0.9 ± 3.7 (−1.6, −0.2)[a]	−2.3 ± 2.1[a] [29.8 (25)]	3.2 ± 2.3 (141)	2.6 ± 1.9 (117)	−0.3 ± 1.6 (−0.6,0.0)[a]	−1.6 ± 0.9[a] [28.8 (23)]
HbA1C (%)	5.5 ± 0.3 (136)	5.5 ± 0.3 (117)	−0.0 ± 0.2 (−0.1,0.0)	−0.3 ± 0.2[a] [38.5 (15)]	5.5 ± 0.3 (141)	5.5 ± 0.3 (117)	−0.0 ± 0.2 (−0.0,0.0)	−0.2 ± 0.2[a] [18.9 (7)]
TG (mg/dL)	111.5 ± 55.8 (136)	102.1 ± 43.9 (118)	−8.4 ± 39.3 (−15.6, −1.1)[a]	−67.5 ± 37.2[a] [57.9 (11)]	110.1 ± 50.5 (139)	95.9 ± 38.3 (121)	−8.4 ± 28.9 (−13.7, −3.1)[a]	−57.5 ± 25.4[a] [47.1 (8)]
HDL-C (mg/dL)	56.3 ± 14.9 (136)	57.2 ± 14.3 (118)	0.5 ± 9.2 (−1.1, 2.2)	12.5 ± 10.7[a] [16.4 (12)]	54.6 ± 15.3 (139)	55.9 ± 13.9 (121)	1.3 ± 7.5 (−0.0,2.7)[a]	11.4 ± 5.4[a] [12.0 (10)]

Abnormality was defined as FPG≥100 **mg/dL**, Insulin >24.9 **uIU/mL**, HOMA-IR>1.9, HBA1C ≥ 5.7 %, HDL-C<60 **mg/dL**, TG ≥ 150 **mg/dL**.
Abbreviations: FPG, Fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycated hemoglobin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; CI, confidence interval.
[a] Significant change from baseline.
[b] The data represent subgroup of participants shifting from abnormal to normal levels and include the mean change from baseline to week 24 in the examined parameter for the subgroup of participants, % of participants shifting to normal and the number of shifters.

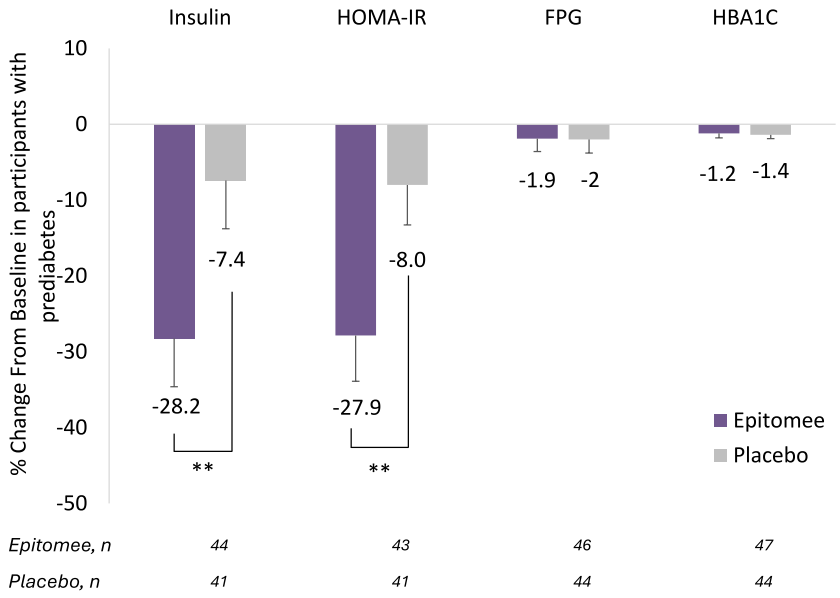

Fig. 3. Changes in metabolic parameters among participants with prediabetes. Percent change from baseline at week 24 in Insulin, HOMA-IR, Fasting plasma glucose (FPG) and glycated hemoglobin (HbA1C) for participants on the Epitomee group compared to placebo. **p < 0.01.

treated with Epitomee compared to placebo group (p < 0.007 and p < 0.003, respectively). These significant differences between the groups were not observed for FPG and HbA1C. Although not significant, at week 24, 38.6 % of the participants from the Epitomee group diagnosed with prediabetes at baseline, shifted to normoglycemia compared to 22.0 % in the placebo group [p = 0.099].

3.3. Analysis of participants with metabolic syndrome

Of the 240 participants completing the RESET study, 58 (24.2 %) participants met the definition of having MetS at baseline. Baseline demographics for this subgroup of participants are presented in Supplemental Table S3. Of the 27 participants in the Epitomee group with MetS at baseline, 16 (59.3 %) no longer had 3 or more diagnostic components of the MetS at week 24. This was not significantly different from the 16 of 31 participants (51.6 %) in the placebo group who no longer had 3 or more diagnostic components of the MetS [p = 0.5598] (Supplemental Fig. S2).

Among those with MetS at baseline, the Epitomee capsule treatment group had significantly greater percent weight reduction than the placebo group [−8.3 ± 7.5 % vs −5.2 ± 4.2 %, respectively; p < 0.0004] (Fig. 4). Of those with MetS, similar proportions of participants in the

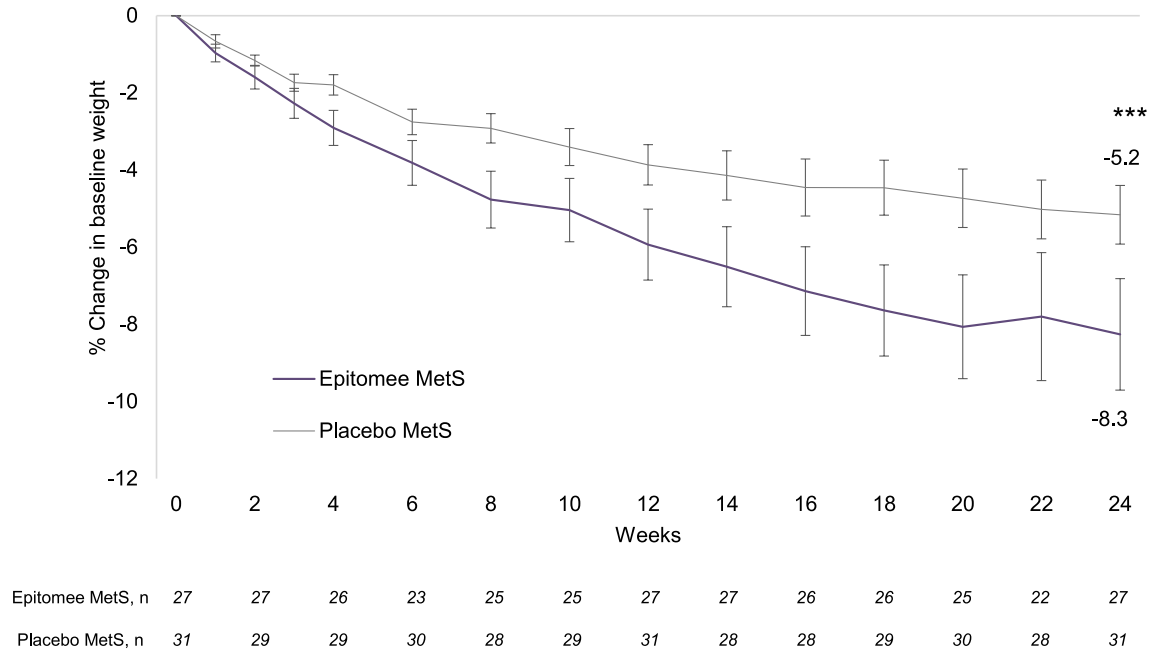

Fig. 4. Weight reduction in participants with Metabolic syndrome (MetS) at baseline to week 24. Participants in the Epitomee group (n = 27) experienced significantly greater weight reduction ($p < 0.0004$) compared to those in the placebo group (n = 31). ***$p < 0.0001$.

Epitomee and placebo groups had a ≥5 % weight reduction at week 24 (59.3 % and 54.8 %, respectively). However, 40.7 % of those receiving Epitomee had ≥10 % weight reduction, compared to only 6.5 % of placebo participants ($p < 0.002$).

4. Discussion

This secondary and exploratory analysis of the randomized, placebo controlled, double-blind, 24-week RESET trial closely examined the effects of 24 weeks of Epitomee or placebo treatment along with lifestyle intervention on individual and clustered cardiometabolic risk factors. RESET study results demonstrated that weight reduction led to improvements in cardiometabolic risk factors in both groups, with no significant difference between the groups. Our analysis showed that both the Epitomee and placebo groups had statistically significant decreases over time in waist circumference, systolic and diastolic blood pressure and in lipid and glycemic parameters. However, for those with prediabetes, HOMA IR and insulin levels were significantly greater with Epitomee compared to placebo. We also demonstrated significant differences in the subpopulation of RESET with MetS at baseline, where Epitomee treatment was associated with significantly greater mean weight loss (−8.3 % vs. −5.2 %) and achievement of 10 % or greater weight loss (40.7 % vs. 6.5 %).

Randomized controlled trials (RCTs) show weight reduction (such as through lifestyle interventions and enhanced physical activity levels) results in reduce insulin resistance, improve glycemic control, reduce blood pressure and improve lipid profiles [12], [13]. A notable example is the Look AHEAD study [14] of over 5000 individuals diagnosed with type 2 diabetes, who had an average baseline BMI of 36. Decreases in fasting glucose, HbA1c levels, TG and SBP observed in the Look AHEAD study, even with modest weight reduction of 2–5%, which may explain the improvements observed in this study placebo group. However, greater weight reduction was related to greater improvements in glycemic control. Also, DBP and HDL-C improvements seemed to require at least a weight reduction between 5 and 10 %. The improvement in these cardiometabolic metrics seemed to be proportional to the degree of weight reduction, with greater weight reduction correlating with greater benefits in CVD risk factor management [14].

The majority of the patient population in the present study did not have abnormalities in the cardiometabolic parameters measured at baseline. This may have reduced the likelihood of achieving statistically significant differences in risk factor improvement between the Epitomee and placebo groups. However, subgroup analyses in participants with prediabetes indicated even greater improvements with Epitomee. Participants with prediabetes treated with Epitomee capsule showed a significant decrease in HOMA-IR and insulin levels compared to placebo. This effect was not observed for FPG and HbA1C; however, 38.6 % of participants in the Epitomee group shifted from prediabetes to normoglycemia compared to only 22.0 % placebo group.

Treatment guidelines generally advocate for weight reduction among patients with obesity or overweight with metabolic complications, ranging from 5 % to 10 % or more, for the purpose of reducing cardiometabolic risk factors and potentially improving health outcomes [15]. Even just a 5 % reduction in body weight can lead to health advantages, such as the improvement or prevention of metabolic disorders [16]. In the overall study population of the RESET study, more than half of the total population (56 %) achieved a ≥5 % weight reduction from baseline [7]. In the analysis presented here, 59.3 % of the Epitomee participants with MetS at baseline achieved at least 5 % weight reduction from baseline, which was not statistically different from 54.8 % of those with MetS treated with placebo. However, among those with MetS treated with Epitomee, 41 % achieved at least 10 % weight reduction from baseline, which was significantly greater than the 6.5 % in the placebo group. Moreover, mean weight reduction in participants with MetS in the Epitomee group was significantly greater than the placebo group (−8.3% vs −5.2 %, respectively, $p < 0.0004$). Among participants with MetS at baseline, the majority (59.3 % of the Epitomee group and 51.6 % of the placebo group) no longer met the diagnostic criteria for MetS (i.e., having less than 3 diagnostic criteria for MetS at study end or 24 weeks of treatment). Considering the small sample size of participants with MetS these findings would have to be further investigated.

Given the observed weight reduction, favorable safety profile and

subsequent improvement in cardiometabolic parameters, the Epitomee capsule may provide a non-pharmacological, treatment option without the adverse effects associated with other anti-obesity treatments.

5. Limitations

Limitations of this study include the small sample size, short (24 week) duration of treatment, and that some of the analyses were not prespecified prior to study initiation. Given that the majority of the patient population did not have abnormal cardiometabolic parameters at baseline (e.g., elevated blood glucose, elevated blood pressure, elevated blood lipids) this may have limited the potential to achieve statistically significant results between groups. Subgroups exhibiting abnormal baseline values are necessary to demonstrate improvement, but their sample sizes are limited. Future studies investigating the effect of the Epitomee capsule might best include larger study populations having abnormal cardiometabolic parameters at baseline, and be extended to ascertain if the benefits of the Epitomee treatment on weight reduction and associated improvement in MetS risk factors can be maintained over a longer time period.

6. Conclusion

In this prespecified secondary and exploratory analysis of the RESET trial, 24 weeks of treatment with either the Epitomee capsule or a placebo capsule, alongside lifestyle interventions, resulted in weight reduction and concomitant improvements in cardiometabolic risk factors. Nevertheless, in participants with prediabetes, treated with Epitomee, weight loss was associated with a significant reduction in HOMA-IR and insulin levels, compared to those receiving placebo. Furthermore, weight reduction in participants with MetS was significantly greater in those treated with Epitomee.

With its favorable safety and tolerability profile, the Epitomee capsule may be an addition to the therapeutic toolbox for weight reduction, potentially improving glycemic control and other cardiometabolic risk factors (e.g., MetS and its metabolic components).

6.1. Key takeaways

- In the entire RESET study population weight loss in both the Epitomee and the placebo groups, resulted in concomitant improvements in cardiometabolic risk factors.
- Epitomee treatment can potentially improve glycemic control in participants with prediabetes and promote significantly greater weight loss in participants with MetS.
- Integrating Epitomee into the therapeutic toolbox for weight reduction can be beneficial for individuals with overweight and obesity.

Author contribution

Harold E. Bays: investigation, writing the original draft, and reviewing and editing the draft; Jamy D. Ard: investigation and reviewing and editing the draft; Patrick M. O'Neil: methodology, investigation, resources, and reviewing and editing the draft; Thomas A. Wadden: investigation, resources, and reviewing and editing the draft; Robert F. Kushner: investigation, conceptualization, methodology, investigation, and reviewing and editing the draft; John M. Jakicic: investigation and reviewing and editing the draft; Holly R. Wyatt: investigation and reviewing and editing the draft; Frank L. Greenway: investigation and reviewing and editing the draft; Moshe Kamar: investigation, reviewing and editing the draft; Eti Ganon-Elazar: investigation, data curation, formal analysis, reviewing and editing the draft, visualization, and data administration; Liora Asaraf Cohen: data curation, formal analysis, reviewing and editing the draft, visualization, and data administration; Donna H. Ryan: conceptualization, writing the original draft, and reviewing and editing the draft.

Ethical adherence and ethical review

This prospective clinical trial involved interventions affecting human test subjects, was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and received approval by independent ethics committees or institutional review boards at each study site. All participants provided written informed consent. The study protocol was registered on clinicaltrials.gov (NCT04222322).

Unless otherwise stated, responsibility for editorial decisions and peer review process for this article was delegated to non-author Editors or non-author Associate Editors.

Declaration of artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this work the authors did not use AI assisted technologies.

Source of funding

This study was founded by Epitomee Medical Ltd, Israel.

Declaration of competing interest

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, Novo-Nordisk, 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.

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.

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.

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.

Robert F. Kushner has received grant support from Epitomee Medical Ltd, received consulting fees from Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Stucture, Altimmune, Regeneron, Currax, and Weight Watchers, and holds a voluntary committee membership position at the American Diabetes Association.

John M. Jakicic has received grant support from Epitomee Medical Ltd and the National Institutes of Health, consulting fees from Scientific Advisory Committee for Wondr Health, Inc., and holds a volunteer leadership position at the American College of Sports Medicine.

Holly R. Wyatt has received grant support from Epitomee Medical Ltd, General Mills, Novo Nordisk, Gelesis, and the National Cattleman's Beef Association, royalites or licenses from State of Slim (book), IP

owned by Shakabuku, and IP licensed to 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.

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 11,534,442, US 11,058,662, US 10,897,921, US 10,507,194, US 9,999,601, US 8,334,000, US 7,709031, US 17/245,538, and US 15/565,367), and stock or stock options from Pep – 19, Slim Health Nutrition, Rejuvenate Bio, Energesis, Ketogenic Health System, GATC Health, and Uplifting Results Inc.

Moshe Kamar received consulting fees from Epitomee.

Eti Ganon-Elazar is an employee of Epitomee Medical Ltd and holds stock options.

Liora Cohen Asaraf is an employee of Epitomee Medical Ltd and holds stock options.

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Appendix A. Supplementary data

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