

Instructions for Use

Rx only

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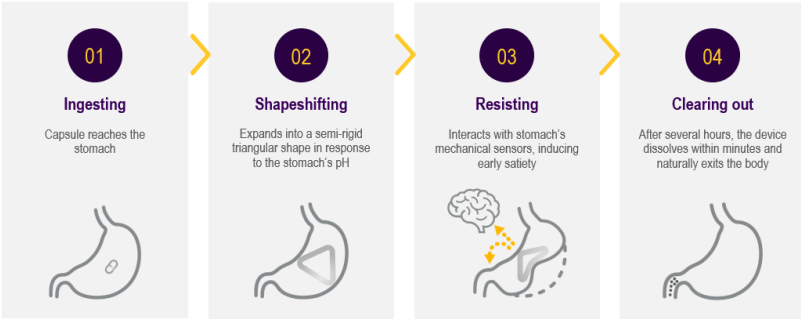
1. PRODUCT DESCRIPTION

Epitomee® is an oral capsule that promotes fullness and may help to increase satiety to help patients manage their weight. Epitomee® is nonsystemic and works directly in the stomach. Epitomee® is made of superabsorbent hydrogel particles enclosed within compartments that are inflated to form a three-dimensional triangular shaped matrix, designed to occupy volume in the stomach, to promote fullness and help patients to manage their weight. Patients consume 2 capsules per day with water before both lunch and dinner.

In the stomach, the superabsorbent particles within the compartments efficiently absorb water and swell, leading to the expansion of the compartments to the final triangular shape. Epitomee® is designed to occupy minimal volume at relatively large dimensions. It is designed to be small enough to move freely within the resting stomach but large enough with sufficient rigidity to be able to resist, withstand, and push softly against the motility waves of the stomach wall to promote satiety and fullness.

Epitomee® passes through the digestive system, maintaining its three-dimensional structure in the stomach, before breaking down in the small intestine, allowing the gel particles to flow down the gastrointestinal (GI) tract and eliminate through normal bowel movements.

Figure 1 below shows the **Epitomee®** ingestion and how it passes through the GI tract.



1.1 How Supplied

Epitomee® is supplied in a carton box containing either 1 blister pack or 4 blister packs. The blister pack holds 14 capsules, each capsule to be administered with water before lunch and dinner.

Figure 2. Epitomee® blister pack



1.2 Storage

- Epitomee® blister pack should be kept closed and stored between 15°C and 25°C (59°F - 77°F).

- Epitomee® should be kept in the original blister pack until use.

2. INDICATIONS FOR USE

Epitomee® is indicated to facilitate weight loss in patients aged 18 and older who are overweight (BMI 25-30 kg/m2) or obese (BMI 30-40 kg/m2) who have not achieved desired results through diet and exercise. Epitomee® is intended to be used as an adjunct to diet and exercise

3. CONTRAINDICATIONS

Epitomee® is contraindicated in the following conditions:

- Pregnancy
- History of allergic reaction to one or more of the device components: cross-linked Polyacrylic acid sodium salt, Hydroxy Propyl Methyl Cellulose (HPMC), Titanium dioxide, Cellulose Acetate Phthalate, Hydroxypropyl Cellulose, Chitosan (vegan), Diethyl Phthalate, Triethyl Citrate, Cellulose Acetate, Acetyl Tributyl Citrate, polyvinyl alcohol polyethylene copolymer.

4. WARNINGS



Read the package insert in its entirety before using Epitomee®.



Keep out of reach of children.



Epitomee® may affect the absorption of medications.
Please review Section 6 carefully.



Do not use Epitomee® after the expiration date printed on product packaging.

5. PRECAUTIONS

- Patients should contact a healthcare provider (HCP) immediately if a severe or continued adverse event occurs. If a severe allergic reaction or severe abdominal pain occurs; patients should discontinue the product until speaking with an HCP.
- Patients with symptoms of dysphagia that may affect ability to swallow capsules are likely to have difficulty swallowing the capsule.
- Do not consume Epitomee® if the package is damaged.
- If any capsule is broken, crushed, or damaged, they should be discarded.
- Use with caution in patients with active gastrointestinal conditions such as gastro-esophageal reflux disease (GERD), ulcers, or heartburn.
- Avoid using in patients with the following conditions:
  - Esophageal anatomic anomalies, including webs, rings, and diverticula.
  - Suspected strictures (such as patients with Crohn's disease).
  - Complications from prior gastrointestinal surgery could affect GI transit and motility.
- Epitomee® is NOT a food substitute. It is not absorbed by the body and therefore has no nutritional or caloric value.
- Epitomee® should be taken under the direction of a health care provider as part of a structured weight loss program. Failure to adhere to prescribed dietary and exercise instructions may result in failure to lose weight.

6. DIRECTIONS FOR USE

Epitomee® should be taken with water twice a day, 30 minutes before the main meals (preferably lunch and dinner). Each dose includes 1 capsule provided in a blister tray.

For each dose, patients should follow these steps:

1. Pull out the Epitomee® capsule from its original package prior to use.
2. Swallow the capsule with 2 cups of water (8 fl oz/250 ml each).
3. Wait 30 minutes to begin the meal.

If a pre-meal dose is missed, instruct the patient to take Epitomee® during or that meal while following the directions for use and swallow one capsule with two glasses of water.

To avoid impact on the absorption of medications:

- The effect of concurrent use of Epitomee® on all medications is not known. Therefore, all medications that are taken once daily should be taken either before taking the Epitomee® capsule in the morning (fasting or with breakfast) or after taking the Epitomee® capsule at bedtime and as prescribed by the physician.
- For all medications that should be taken with food, the medication should be taken after the meal has started.

7. COMPONENTS INFORMATION

Epitomee® capsule contains 339 mg of cross-linked polyacrylic acid sodium salt.

8. POTENTIAL ADVERSE REACTIONS

Adverse effects have been monitored in the RESET pivotal trial, during the 28 weeks of the trial period. The overall incidence of adverse events with Epitomee® treatment was no different than the placebo (86.2% in Epitomee® and 84.4% in the placebo group, respectively). In both treatment groups, most (>95%) adverse events were assessed by the investigator as mild or moderate in intensity. The number of patients with any adverse event leading to study withdrawal was lower with Epitomee® compared to the placebo. There were no serious adverse device effects (SADEs) in the study. None of the two serious treatment-emergent AEs that occurred in the study were related to the study treatment. No deaths occurred during the trial. Gastrointestinal adverse events rates were similar between Epitomee® and the placebo treatments.

Observed and potential GI adverse effects associated with the use of Epitomee® are listed below.

Table 1. Potential GI Adverse Events (rates observed compared to placebo)*

Greater than Placebo	Lower than Placebo	Equal to Placebo	Not observed
• Abdominal discomfort (pain, cramping)	• Constipation • Nausea • Abdominal distension (bloating) • Flatulence • GERD • Vomiting	• All GI adverse events combined (93.5% mild) • Diarrhea	• Adverse health consequences resulting from weight loss • Allergic Reaction • Bowel obstruction • Choking • Death • GI atonia or hypomotility • Interaction with other medication • Need for emergency surgery

*Rates observed in the RESET pivotal study

9. CLINICAL STUDIES

The safety and effectiveness of Epitomee® was studied in the 6 month RESET pivotal trial.

9.1 Study Design

The Randomized Evaluation of Efficacy and Safety of Epitomee® capsule Trial RESET (ClinicalTrials.gov, NCT04222322) was a multicenter, prospective, randomized, double-blind, placebo-controlled trial assessing the safety and efficacy of Epitomee® on body weight over 24 weeks in 279 overweight and obese subjects (with or without pre-diabetes). Subjects were randomized to Epitomee® or Placebo groups. All subjects received a moderate intensity lifestyle intervention program throughout the trial duration.

Enrollment included patients ≥ 18 years. Patients with pre-diabetes were required to have either one or both of the following criteria: FPG ≥100 mg/dL and <126 mg/dL, and/or HbA1c ≥5.7% and ≤6.4%, and untreated or on stable dose of metformin (dose of up to 2000 mg/dL) for at least 4 months. Patients with comorbidities (dyslipidemia or hypertension) had to be stable on their hypertension and lipid modifying medications. Patients were excluded if pregnant, had Type I or Type II diabetes, advanced cardiac disease, chronic steroids treatment or known history of gastrointestinal or endocrine disease.

9.2 Study Endpoints

The primary objectives were to compare the 24-week weight loss achieved with the Epitomee® combined with a moderate intensity lifestyle intervention program to that achieved with a visually matching placebo combined with moderate intensity lifestyle intervention program.

The Co-primary effectiveness endpoints were:

- A comparison of the difference between the average body weight loss at 24-weeks post randomization between the Epitomee® and placebo groups.

- The proportion of treatment responders, i.e., subjects among the Epitomee® group, who have at least lost 5% weight from baseline, at 24-weeks post randomization.

The safety endpoint was the incidence of all adverse events (AEs) and serious adverse events (SAEs) in an analysis of the safety population, defined as the cohort including all subjects who took at least one study capsule of Epitomee® or placebo after randomization.

The Co-primary effectiveness endpoints were included in the Full Analysis Set (FAS) population defined the cohort of all randomized subjects, who consumed at least one study capsule post-randomization and have completed baseline and at least one post-baseline assessment of weight.

FAS served as the primary analysis set for the primary efficacy assessment. PP #1 (defined as a subset of the FAS which includes subjects who dad no major protocol violations and were compliant with capsule intake of at least 75%, and PP #2 (defined as a subset of the FAS which includes subjects who dad no major protocol violations and were compliant with capsule intake of at least 85%) were used for co-primary, secondary, and supportive analyses. The safety analysis set served for analysis of all safety endpoints.

9.3 Study Population Demographics and Baseline Characteristics

A total of 444 subjects were screened for eligibility to participate in the trial. Of these candidates, 279 were randomized 1:1 to receive Epitomee® (138) or placebo (141). A total of 39 subjects were terminated early during the study course, including 19 (13.8%) and 20 (14.2%) subjects, in Epitomee® and placebo group, respectively. Accordingly, 240 subjects completed the study, 119/138 in Epitomee® group and 121/141 in the placebo group. Of the terminated subjects, 12 (4.3%) subjects withdrew their consent (6 from each group) during the study; personal reasons were cited as being most common. Nine subjects were lost to follow-up without specifying reasons for their decision 7 (5.1%) and 2 (1.4%) subjects from Epitomee® and placebo groups, respectively. Study treatment was discontinued in 2 (1.4%) and 5 (3.5%) subjects from Epitomee® and placebo groups, respectively, due to adverse events **(Table 2).**

Table 2. Rate of dropouts by primary reasons

Reason for Discontinuation from Study	Treatment group			
	Epitomee® (n=138)		Placebo (n=141)	
	N	%	N	%
Adverse Event	2	10.53	5	25.00
Consent withdrawal	6	31.58	6	30.00
Investigator's request	0	0.00	1	5.00
Lost to follow-up/ failure to return	7	36.84	2	10.00
Major protocol deviation	0	0.00	2	10.00
Non-compliance	2	10.53	2	10.00
Other	0	0.00	2	10.00
Pregnancy	2	10.53	0	0.00

The majority of subjects in both groups were Caucasian, (70.3% and 65.2% in Epitomee® and placebo groups, respectively); Black or African American subjects constituted 21.0% and 24.1% of the total sample in the Epitomee® and placebo groups, respectively.
The groups were evenly matched for gender and age (**Table 3**). Most subjects were females (80.4% and 79.4% in Epitomee® and placebo groups, respectively) between 40 and 65 years of age (mean age 48.5 and mean BMI 34.1 in Epitomee® group; mean age 48.6 and mean BMI 33.7 in the placebo group) (66.7% and 67.4% in Epitomee® and placebo groups, respectively). The mean weight at enrollment was 95.9 Kg (211.4 lbs) in the Epitomee® group and 95.7 Kg (211.0 lbs) in the placebo group. Average waist circumference was 106.7 cm in Epitomee® group and 107.6 cm in the placebo group. subjects were matched between groups for their glycemic status at randomization with 57.2 % and 63.8% of the subjects being normoglycemic in Epitomee® and control groups, respectively and 39.1% and 35.5% being prediabetic in the Epitomee® and placebo groups, respectively. Hypertension was present in 27.5% of Epitomee® subjects compared to 24.8% of the placebo group (**Table 3)**.

Table 3. Summary of Subject Demographic and Baseline Characteristics – FAS Population

	Epitomee® N=138	**Placebo N=141**	**Difference (95% CI) [1]**	**P-Value [2]**
Age (years), Mean ± SD (N)	48.5 ± 12.5 (138)	48.6 ± 12.4 (141)	-0.1 (-3.1 ,2.8)	0.9222
Gender, % (n/N)				0.8818
Female	80.4% (111/138)	79.4% (112/141)	1.0% (-8.4%, 10.4%)	
Male	19.6% (27/138)	20.6% (29/141)	-1.0% (-10.4%, 8.4%)	
Race/Ethnicity, % (n/N)				0.6050
Caucasian	70.3% (97/138)	65.2% (92/141)	5.0% (-5.9%, 16.0%)	
Black or African-American	21.0% (29/138)	24.1% (34/141)	-3.1% (-12.9%, 6.7%)	
Hispanic\Latino	2.2% (3/138)	0.7% (1/141)	1.5% (-1.3%, 4.3%)	
Asian	1.4% (2/138)	3.5% (5/141)	-2.1% (-5.7%, 1.5%)	
American Indian or Alaska Native	0.7% (1/138)	1.4% (2/141)	-0.7% (-3.1%, 1.7%)	
Multiple Race	2.9% (4/138)	5.0% (7/141)	-2.1% (-6.6%, 2.5%)	
Unknown/ Not Reported	1.4% (2/138)	0.0% (0/141)	1.4% (-0.5%, 3.4%)	
Weight (kg), Mean ± SD (N)	95.9 ± 15.4 (138)	95.7 ± 15.4 (141)	0.1 (-3.5 ,3.8)	0.9409
Height (cm), Mean ± SD (N)	167.3 ± 9.1 (138)	168.2 ± 8.7 (141)	-0.9 (-3.0 ,1.2)	0.4135
BMI (kg/m^2), Mean ± SD (N)	34.1 ± 3.3 (138)	33.7 ± 3.4 (141)	0.4 (-0.4 ,1.2)	0.3197
Waist Circumference (cm), Mean ± SD (N)	106.7 ± 11.1 (138)	107.6 ± 11.7 (141)	-0.9 (-3.6 ,1.8)	0.5124
Weight Categories, % (n/N)				0.1454
Overweight	9.4% (13/138)	16.3% (23/141)	-6.9% (-14.7%, 0.9%)	
Obese Class I	47.8% (66/138)	44.7% (63/141)	3.1% (-8.6%, 14.8%)	
Obese Class II	39.1% (54/138)	38.3% (54/141)	0.8% (-10.6%, 12.3%)	
Obese Class III	3.6% (5/138)	0.7% (1/141)	2.9% (-0.5%, 6.3%)	

	Epitomee® N=138	**Placebo N=141**	**Difference (95% CI) [1]**	**P-Value [2]**
Comorbidities, % (n/N)				0.8082
Diabetes	0.7% (1/138)	0.7% (1/141)	0.0% (-2.0%, 2.0%)	
Cardiovascular	41.3% (57/138)	39.7% (56/141)	1.6% (-9.9%, 13.1%)	
Hypertension	27.5% (38/138)	24.8% (35/141)	2.7% (-7.6%, 13.0%)	
Metabolic Syndrome	13.8% (19/138)	16.3% (23/141)	-2.5% (-10.9%, 5.8%)	
LDL Cholesterol (mg/dL), Mean ± SD (N)	116.5 ± 31.4 (136)	117.0 ± 31.2 (139)	-0.5 (-8.0 ,6.9)	0.8885
HDL Cholesterol (mg/dL), Mean ± SD (N)	56.3 ± 14.9 (136)	54.6 ± 15.3 (139)	1.8 (-1.8 ,5.3)	0.3352
Systolic Blood Pressure (mmHg), Mean ± SD (N)	120.9 ± 14.2 (138)	121.1 ± 13.4 (141)	-0.1 (-3.4 ,3.1)	0.9311
Diastolic Blood Pressure (mmHg), Mean ± SD (N)	77.3 ± 10.6 (138)	77.9 ± 9.2 (141)	-0.6 (-2.9 ,1.7)	0.6124
Fasting Glucose (mg/dL), Mean ± SD (N)	91.3 ± 10.9 (135)	91.6 ± 10.1 (137)	-0.2 (-2.7 ,2.3)	0.8530
Smoking, % (n/N)	2.2% (3/138)	2.1% (3/141)	0.0% (-3.4%, 3.5%)	1.0000

[1] Difference taken for comparability between the two groups. 95% Confidence interval and p-value for the difference in means (or proportions). Confidence intervals and p-values are not adjusted for multiple comparisons.

[2] The T-Test was applied for continuous variables and the Fisher exact test for the categorical variables.

9.4 Safety

The safety endpoints were analyzed on the safety population, defined as the cohort including any subject receiving either Epitomee® or placebo after randomization, for all AEs and SAEs (total of 279; n=138 for Epitomee® and n=141 for placebo).

Epitomee® treatment was well tolerated, with fewer patients' dropouts in Epitomee® group than the placebo group:19 (13.8%) and 20 (14.2%), respectively. Only 2 (1.5 %) of Epitomee® patients discontinued from the study due to adverse events compared to 5 (3.6%) patients from the placebo group (**Table 4)**. Nine subjects were lost to follow up without specifying reasons for their decision and without reports of safety related events, 7 (5.1%) from the Epitomee® group and 2 (1.4%,) from the placebo group.

Table 4 Summary of AEs resulting in subjects' withdrawal based on MedDRA's system organ class and relatedness.

	Epitomee® (N=138)	Placebo (N=141)
	Number of subjects with event (% (n))	Number of subjects with event (% (n))
All Adverse events	1.5% (2)	3.6% (5)
Gastrointestinal disorders	0.7% (1)	2.8% (4)
Related	0.7% (1)	2.1% (3)
Infections and infestations	0% (0)	0.7% (1)
Related	0% (0)	0.7% (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.7% (1)	0% (0)

There were no differences in the incidence of AEs between the study groups. Adverse events were equally distributed between the groups when assessed by severity. In both groups, almost all adverse events were assessed by the investigator as mild or moderate in intensity (>95%). There were no serious adverse device effects (SADEs) in the study. There were two serious AEs that occurred in the study, one in each group, neither of which was related to the study treatment. No deaths occurred in the trail (**Table 5)**.

Table 5. Summary of Treatment-Emergent Adverse Events by treatment group – Safety Population

	Epitomee® (N=138)		Placebo (N=141)	
	Number Events	Number Subjects with Event [%(n/N)]	Number Events	Number Subjects with Event [%(n/N)]
Number of Subjects with any AE	357	86.2% (119/138)	368	84.4% (119/141)
Grade 3 (Severe)	16	8.7% (12/138)	18	7.8% (11/141)
Grade 2 (Moderate)	97	37.0% (51/138)	92	34.8% (49/141)
Grade 1 (Mild)	244	77.5% (107/138)	258	77.3% (109/141)
Serious Treatment Adverse Event	1	0.7% (1/138)	1	0.7% (1/141)
Number of AE's leading to withdrawal	2	1.4% (2/138)	5	3.5% (5/141)
Death	0	0.0% (0/138)	0	0.0% (0/141)

There were no differences in the incidence of AEs between the groups in relation to causality, AE outcome, and action taken. In both the Epitomee® and the Placebo groups, most adverse events were assessed as unrelated to the investigational device (295/357 (82.6%) and 285/368 (77.4%), respectively).
Infections and infestations, such as infections of the respiratory tract, (i.e. common cold and COVID-19) affected the highest number of subjects in the study and were reported for similar proportions of subjects in both study groups (45.7% and 45.4% in the Epitomee® and placebo group, respectively) (**Table 6**).
A summary of treatment-emergent events that occurred in at least 2% of the subjects in the safety analysis set is presented in **Table 7** by SOC, preferred term (PT), and severity.

Table 6: All treatment emergent AEs summarized by SOC, relatedness and treatment group – safety population

	Epitomee® (N=138)		Placebo (N=141)	
	# Events	Number Subjects with Event [%(n/N)]	# Events	Number Subjects with Event [%(n/N)]
All Adverse Events	357	86.2% (119/138)	368	84.4% (119/141)
Not related	295	80.4% (111/138)	285	77.3% (109/141)
Related	62	30.4% (42/138)	83	34.8% (49/141)
Blood and lymphatic system disorders	4	2.9% (4/138)	2	1.4% (2/141)
Not related	4	2.9% (4/138)	2	1.4% (2/141)
Cardiac disorders	2	1.4% (2/138)	3	0.7% (1/141)
Not related	2	1.4% (2/138)	3	0.7% (1/141)
Ear and labyrinth disorders	2	0.7% (1/138)	2	1.4% (2/141)
Not related	2	0.7% (1/138)	2	1.4% (2/141)
Eye disorders	4	2.9% (4/138)	1	0.7% (1/141)
Not related	4	2.9% (4/138)	1	0.7% (1/141)
Gastrointestinal disorders	83	39.1% (54/138)	98	40.4% (57/141)
Not related	32	12.3% (17/138)	24	8.5% (12/141)
Related	51	26.8% (37/138)	74	31.9% (45/141)
General disorders and administration site conditions	14	9.4% (13/138)	19	10.6% (15/141)
Not related	13	8.7% (12/138)	18	9.9% (14/141)
Related	1	0.7% (1/138)	1	0.7% (1/141)
Hepatobiliary disorders	1	0.7% (1/138)	0	0.0% (0/141)
Not related	1	0.7% (1/138)	0	0.0% (0/141)
Immune system disorders	8	5.8% (8/138)	4	2.8% (4/141)
Not related	8	5.8% (8/138)	4	2.8% (4/141)
Infections and infestations	88	45.7% (63/138)	87	45.4% (64/141)
Not related	85	43.5% (60/138)	86	44.7% (63/141)
Related	3	2.2% (3/138)	1	0.7% (1/141)

	Epitomee® (N=138)		Placebo (N=141)	
	# Events	Number Subjects with Event [%(n/N)]	# Events	Number Subjects with Event [%(n/N)]
Injury, poisoning and procedural complications	23	13.8% (19/138)	21	12.8% (18/141)
Not related	23	13.8% (19/138)	21	12.8% (18/141)
Investigations	26	13.0% (18/138)	19	8.5% (12/141)
Not related	21	10.1% (14/138)	15	6.4% (9/141)
Related	5	2.9% (4/138)	4	2.1% (3/141)
Metabolism and nutrition disorders	11	7.2% (10/138)	9	5.7% (8/141)
Not related	11	7.2% (10/138)	9	5.7% (8/141)
Musculoskeletal and connective tissue disorders	23	14.5% (20/138)	40	20.6% (29/141)
Not related	23	14.5% (20/138)	39	19.9% (28/141)
Related	0	0.0% (0/138)	1	0.7% (1/141)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	2.9% (4/138)	2	1.4% (2/141)
Not related	4	2.9% (4/138)	2	1.4% (2/141)
Nervous system disorders	21	10.9% (15/138)	16	8.5% (12/141)
Not related	20	10.1% (14/138)	15	7.8% (11/141)
Related	1	0.7% (1/138)	1	0.7% (1/141)
Pregnancy, puerperium and perinatal conditions	3	1.4% (2/138)	0	0.0% (0/141)
Not related	3	1.4% (2/138)	0	0.0% (0/141)
Psychiatric disorders	6	3.6% (5/138)	1	0.7% (1/141)
Not related	6	3.6% (5/138)	1	0.7% (1/141)
Renal and urinary disorders	0	0.0% (0/138)	3	1.4% (2/141)
Not related	0	0.0% (0/138)	3	1.4% (2/141)
Reproductive system and breast disorders	8	5.1% (7/138)	5	2.8% (4/141)
Not related	8	5.1% (7/138)	5	2.8% (4/141)

	Epitomee® (N=138)		Placebo (N=141)	
	# Events	Number Subjects with Event [%(n/N)]	# Events	Number Subjects with Event [%(n/N)]
Respiratory, thoracic and mediastinal disorders	13	8.0% (11/138)	20	10.6% (15/141)
Not related	12	7.2% (10/138)	20	10.6% (15/141)
Related	1	0.7% (1/138)	0	0.0% (0/141)
Skin and subcutaneous tissue disorders	8	5.8% (8/138)	6	3.5% (5/141)
Not related	8	5.8% (8/138)	5	2.8% (4/141)
Related	0	0.0% (0/138)	1	0.7% (1/141)
Surgical and medical procedures	2	1.4% (2/138)	5	3.5% (5/141)
Not related	2	1.4% (2/138)	5	3.5% (5/141)
Vascular disorders	3	2.2% (3/138)	5	2.8% (4/141)
Not related	3	2.2% (3/138)	5	2.8% (4/141)

Table 7. Summary of Treatment-Emergent Adverse Events (PT with at least 2% of the study population) by Preferred Term, and Severity – Safety Population

	Epitomee (N=138)		Placebo (N=141)	
	Number Events	Number Subjects with Event [%(n/N)]	Number Events	Number Subjects with Event [%(n/N)]
All Adverse Events	357	86.2% (119/138)	368	84.4% (119/141)
Gastrointestinal disorders				
Abdominal discomfort	7	5.1% (7/138)	4	2.1% (3/141)
Mild	6	4.3% (6/138)	2	0.7% (1/141)
Moderate	1	0.7% (1/138)	2	1.4% (2/141)
Abdominal distension	5	3.6% (5/138)	13	7.1% (10/141)
Mild	4	2.9% (4/138)	11	5.7% (8/141)
Moderate	1	0.7% (1/138)	2	1.4% (2/141)

	Epitomee (N=138)		Placebo (N=141)	
	Number Events	Number Subjects with Event [%(n/N)]	Number Events	Number Subjects with Event [%(n/N)]
Abdominal pain	9	6.5% (9/138)	5	2.8% (4/141)
Mild	8	5.8% (8/138)	3	1.4% (2/141)
Moderate	1	0.7% (1/138)	2	1.4% (2/141)
Constipation	16	9.4% (13/138)	24	16.3% (23/141)
Mild	13	7.2% (10/138)	18	12.8% (18/141)
Moderate	2	1.4% (2/138)	5	2.8% (4/141)
Severe	1	0.7% (1/138)	1	0.7% (1/141)
Diarrhoea	7	5.1% (7/138)	9	5.7% (8/141)
Mild	6	4.3% (6/138)	8	5.0% (7/141)
Moderate	1	0.7% (1/138)	1	0.7% (1/141)
Flatulence	2	1.4% (2/138)	7	5.0% (7/141)
Mild	1	0.7% (1/138)	7	5.0% (7/141)
Moderate	1	0.7% (1/138)	0	0.0% (0/141)
Gastrooesophageal reflux disease	2	1.4% (2/138)	4	2.8% (4/141)
Mild	2	1.4% (2/138)	3	2.1% (3/141)
Moderate	0	0.0% (0/138)	1	0.7% (1/141)
Nausea	8	5.8% (8/138)	15	9.9% (14/141)
Mild	7	5.1% (7/138)	13	8.5% (12/141)
Moderate	1	0.7% (1/138)	1	0.7% (1/141)
Severe	0	0.0% (0/138)	1	0.7% (1/141)
General disorders and administration site conditions				
Fatigue	4	2.9% (4/138)	4	2.8% (4/141)
Mild	2	1.4% (2/138)	4	2.8% (4/141)
Moderate	2	1.4% (2/138)	0	0.0% (0/141)
Immune system disorders				
Seasonal allergy	6	4.3% (6/138)	2	1.4% (2/141)
Mild	5	3.6% (5/138)	1	0.7% (1/141)
Moderate	1	0.7% (1/138)	1	0.7% (1/141)
Infections and infestations				
COVID-19	15	10.9% (15/138)	16	11.3% (16/141)

	Epitomee (N=138)		Placebo (N=141)	
	Number Events	Number Subjects with Event [%(n/N)]	Number Events	Number Subjects with Event [%(n/N)]
Mild	10	7.2% (10/138)	13	9.2% (13/141)
Moderate	5	3.6% (5/138)	3	2.1% (3/141)
Gastroenteritis	8	5.8% (8/138)	4	2.8% (4/141)
Mild	5	3.6% (5/138)	3	2.1% (3/141)
Moderate	3	2.2% (3/138)	1	0.7% (1/141)
Gastroenteritis viral	3	2.2% (3/138)	4	2.8% (4/141)
Mild	3	2.2% (3/138)	3	2.1% (3/141)
Moderate	0	0.0% (0/138)	1	0.7% (1/141)
Influenza	3	2.2% (3/138)	3	2.1% (3/141)
Mild	1	0.7% (1/138)	1	0.7% (1/141)
Moderate	2	1.4% (2/138)	2	1.4% (2/141)
Nasopharyngitis	17	10.9% (15/138)	15	9.9% (14/141)
Mild	16	10.1% (14/138)	15	9.9% (14/141)
Moderate	1	0.7% (1/138)	0	0.0% (0/141)
Sinusitis	5	3.6% (5/138)	5	3.5% (5/141)
Mild	3	2.2% (3/138)	2	1.4% (2/141)
Moderate	1	0.7% (1/138)	3	2.1% (3/141)
Severe	1	0.7% (1/138)	0	0.0% (0/141)
Upper respiratory tract infection	19	11.6% (16/138)	14	7.8% (11/141)
Mild	14	8.0% (11/138)	11	5.7% (8/141)
Moderate	4	2.9% (4/138)	2	1.4% (2/141)
Severe	1	0.7% (1/138)	1	0.7% (1/141)
Urinary tract infection	5	3.6% (5/138)	4	2.8% (4/141)
Mild	3	2.2% (3/138)	4	2.8% (4/141)
Moderate	1	0.7% (1/138)	0	0.0% (0/141)
Severe	1	0.7% (1/138)	0	0.0% (0/141)
Injury, poisoning and procedural complications				
Immunisation reaction	3	2.2% (3/138)	3	2.1% (3/141)
Mild	2	1.4% (2/138)	1	0.7% (1/141)
Moderate	1	0.7% (1/138)	1	0.7% (1/141)

	Epitomee (N=138)		Placebo (N=141)	
	Number Events	Number Subjects with Event [%(n/N)]	Number Events	Number Subjects with Event [%(n/N)]
Severe	0	0.0% (0/138)	1	0.7% (1/141)
Investigations				
Low density lipoprotein increased	3	2.2% (3/138)	3	2.1% (3/141)
Mild	3	2.2% (3/138)	3	2.1% (3/141)
Musculoskeletal and connective tissue disorders				
Arthralgia	4	2.9% (4/138)	16	9.2% (13/141)
Mild	3	2.2% (3/138)	11	6.4% (9/141)
Moderate	1	0.7% (1/138)	5	2.8% (4/141)
Back pain	5	3.6% (5/138)	7	5.0% (7/141)
Mild	3	2.2% (3/138)	4	2.8% (4/141)
Moderate	1	0.7% (1/138)	2	1.4% (2/141)
Severe	1	0.7% (1/138)	1	0.7% (1/141)
Nervous system disorders				
Headache	11	6.5% (9/138)	9	5.7% (8/141)
Mild	8	4.3% (6/138)	6	3.5% (5/141)
Moderate	2	1.4% (2/138)	3	2.1% (3/141)
Severe	1	0.7% (1/138)	0	0.0% (0/141)
Respiratory, thoracic and mediastinal disorders				
Cough	5	2.9% (4/138)	4	2.8% (4/141)
Mild	3	2.2% (3/138)	3	2.1% (3/141)
Moderate	2	0.7% (1/138)	1	0.7% (1/141)
Sinus congestion	1	0.7% (1/138)	6	3.5% (5/141)
Mild	1	0.7% (1/138)	6	3.5% (5/141)

All AEs were Coded by investigator verbatim terms using Medical Dictionary for Regulatory Authorities [MedDRA] version 26.0

Subjects with more than one AE are counted only once, at the worst severity.

Gastrointestinal disorders, were nominally lower in the placebo group vs. Epitomee® group, but there were little difference proportions of subjects (39.1% and 40.4% in Epitomee® and placebo group, respectively) (**Table 6)**.

Table 8. Summary of Gastrointestinal Adverse Events by Severity Deemed Possibly Related, Probably Related, and Definitely Related to Investigational Product – Safety Population

	Epitomee® (N=138)		Placebo (N=141)	
	Number Events	Number Subjects with Event [%(n/N)]	Number Events	Number Subjects with Event [%(n/N)]
Gastrointestinal disorders[1]	51	26.8% (37/138)	74	31.9% (45/141)
Mild	39	20.3% (28/138)	60	23.4% (33/141)
Moderate	12	6.5% (9/138)	13	7.8% (11/141)
Severe	0	0.0% (0/138)	1	0.7% (1/141)

[1] Subjects with more than one AE are counted only once, at the worst severity.

No significant difference was observed for serum electrolytes, total proteins, or hematocrit in either group (**Table 9)**.

Table 9. Laboratory values at randomization and week 24 (end of treatment) and change from baseline– Safey population.

	Epitomee® group			Placebo group		
Parameter	Baseline Mean±SD (N)	Week 24 Mean±SD (N)	Change from baseline Mean±SD (CI)	Baseline Mean±SD (N)	Week 24 Mean±SD (N)	Change from baseline Mean±SD (CI)
Sodium (mEq/L)	139.86±2.26 (138)	140.02±2.38 (118)	0.15±2.40 (-0.28, 0.58)	139.51±2.68 (141)	139.73±2.56 (121)	0.12±2.96 (-0.41, 0.66)
Potassium (mEq/L)	4.54±0.49 (138)	4.44±0.44 (115)	-0.07±0.49 (-0.16, 0.02)	4.53±0.51 (141)	4.44±0.42 (121)	-0.09±0.53 (-0.18, 0.01)

Calcium (mg/dL)	9.42±0.41 (138)	9.49±0.40 (118)	0.07±0.39 (0,0.14)	9.34±0.33 (141)	9.34±0.34 (121)	0.01±0.30 (-0.04, 0.07)
Magnesium (mg/dL)	2.07±0.15 (138)	2.07±0.16 (118)	0.01±0.14 (-0.02, 0.03)	2.06±0.16 (141)	2.08±0.17 (121)	0.01±0.18 (-0.02,0.05)
Haematocrit (%)	41.11±3.68 (138)	41.28±3.74 (118)	0.24±2.35 (-0.19, 0.67)	41.23±3.61 (141)	41.39±3.59 (120)	0.12±2.61 (-0.35, 0.59)

No signals of altered absorption of medications were observed based on blood pressure management, while on antihypertensive and low-density lipoprotein cholesterol, while on lipid lowering agents.

Epitomee® was therefore well tolerated with no significant safety concerns compared to placebo.

9.5 *Effectiveness*

9.5.1 Primary End Point Analysis

The study has two co-primary endpoints. Both co-primary endpoints refer to body weight loss at 24-weeks post treatment initiation. The first co primary end point estimates the continuous percent of body weight reduction at 24 weeks following treatment. The other co-primary endpoint analyzes the proportion of patients achieving the performance goal of ≥5% weight loss at week 24.
The co-primary effectiveness end points were analyzed using the FAS (ITT population), which includes all randomized subjects, who consumed at least one study capsule post-randomization and have completed baseline and at least one post-baseline assessment of weight. For this population, data at Week 24 (End of Treatment) was available for 119 cases in the Epitomee® group and 121 cases in the placebo group. Comparison of the difference of the average total body weight loss between groups at 24-weeks post randomization shows greater weight loss at Week 24 for subjects assigned to Epitomee® vs. placebo treatment: 6.6% vs. 4.6%, respectively (**Table 10**).
For the co-primary endpoint I of the percent change in total body weight loss, the hypothesis was tested by first imputing any missing data in percent change in total body weight using multiple imputations, followed by modeling of the LS mean difference between groups at 24 weeks, adjusted for baseline weight (**Table 10**). Based on ITT-MI analysis, the inter-group difference in precent total

body weight loss was statistically significant (*P*<0.0001), allowing to reject the null hypothesis and demonstrate superiority over the placebo group.

Table 10: Co-primary end point I: Percent total body weight loss from baseline to week 24 (end of treatment)

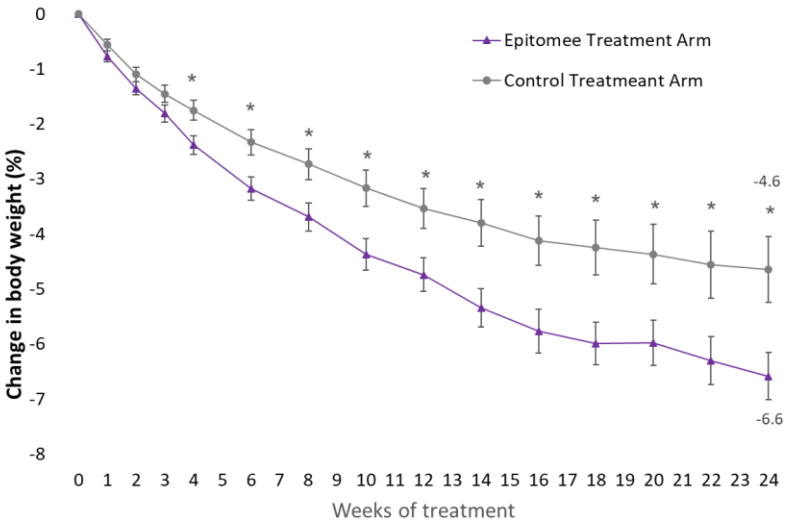
FAS population (ITT)	Epitomee® (n=138)	Placebo (n=141)
Observed data	N observed = 119 N missing =19	N observed = 121 N missing =20
Mean (SD)	6.6 (6.5)	4.6 (4.7)
Median (Min, Max)	6.1 (-7.2, 29.5)	4.4 ((-5.7, 18.9)
MMRM modeling (ITT-MI) – LS mean difference [1]		
Mean ± SE	1.8 (0.5)	
CI (95%)	0.8, I	
P-value **[2]**	<0.0001	
ANCOVA modeling (ITT-MI) – LS mean difference [1]		
Mean ± SE	1.9 (0.7)	
CI (95%)	0.6 , 3.3	
P-value **[2]**	0.0054	
PP1 population	Epitomee® (n=113)	Placebo (n=113)
Observed data	N observed = 113 N missing =0	N observed = 113 N missing =0
Mean (SD)	6.7 (6.5)	4.9 (4.8)
Median (Min, Max)	6.3 (-7.2, 29.5)	4.7 (-5.7, 18.9)
MMRM modeling– LS mean difference		
Mean ± SE	2.0 (0.498)	
CI (95%)	1.2, I	
P-value **[2]**	<0.0001	
PP2 population	Epitomee® (n=110)	Placebo (n=107)

Observed data	N observed = 110 N missing =0	N observed = 107 N missing =0
Mean (SD)	6.9 (6.6)	5.1 (4.8)
Median (Min, Max)	6.4 (-7.2, 29.5)	4.7 (-5.7, 18.9)
MMRM modeling– LS mean difference		
Mean ± SE	2.0 (0.5)	
CI (95%)	1.2, I	
P-value **[2]**	<0.0001	

[1] Multiple Imputations (MI) of missing data.
[2] P-value adjusted for baseline weight.

Figure 3 below presents the mean percent weight change from baseline plotted over time. Weight loss in the Epitomee® group became apparent as early as week 4, with mean percent change in total body weight being significantly greater than the placebo (using ttest). No weight loss plateau was observed during the 24 weeks RESET study and weight loss was sustained during the 24 weeks follow-up period.

Figure 3: Mean overtime of percent change in total body weight from baseline.



# participants	Rando	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Epitomee	138	131	124	128	118	113	119
Control	141	129	126	126	114	119	121

The co-primary endpoint of whether the proportion of responders (%TBW ≥ 5%) with Epitomee® at week 24 is significantly higher than the threshold rate of 35%, was achieved as well (p<0.0001; binominal test based on the ITT-MI see **Table 11**), allowing to reject the null hypothesis. More subjects treated with Epitomee® achieved clinically meaningful weight loss; 55.5% with Epitomee® vs. 44% with placebo.

Table 11. Co-primary end point II analysis: Responder rate (%TBW ≥ 5%) in percentage weight loss at Week 24 (end of treatment)

N observed	N missing	Number of responders	Proportion (%)	Lower bound 95% CI	Upper bound 95% CI	P-Value [1]
FAS population (ITT)						
119	19	66	55.5	46.1	64.6	<0.0001 [2]
PP1 population						
113	0	64	56.6	47.0	65.9	<0.0001
PP2 population						
110	0	63	57.3	47.5	66.7	<0.0001

[1] Binominal test for proportion- compared to 35% threshold.
[2] Multiple imputations of missing data.

9.5.2 Secondary End Point Analysis

The RESET study included several secondary effectiveness end points to investigate the impact of weight loss on additional clinical outcomes.
Epitomee® treatment resulted in a significantly higher percentage of responders losing between 7.5-12.5% of TBW as compared to placebo treatment. Specifically, 38.7% of Epitomee® treated subjects achieved ≥ 7.5%, 26.9% achieved ≥ 10%, and 16.8%, ≥ 12.5% of total body weight loss compared to 21.5%, 10.7% and 6.6% of the placebo group (FAS, Logistic Regression, **Table 12,** and **Table 13**). Additionally, over 10% of Epitomee® subjects lost at least 15% of their body weight as compared to 6% of the placebo subjects. The odds of being ≥ 7.5% and ≥ 10%, body weight responder was 3.1 and 2.3-fold higher with Epitomee® vs. placebo.

Table 12. Frequency distribution of Responder rate in percentage total body weight loss from baseline to week 24 (end of treatment) for different "Cutoff" values– FAS.

Visit	Responder Rate Analysis (Cutoff)	Treatment group*	Number of responders (n)	Proportion (%)
Week 24 - End of Treatment	Percent change in Total Body Weight Responder (%TBW ≥ 3%)	Epitomee®	83	69.7
		Placebo	78	64.5
Week 24 - End of Treatment	Percent change in Total Body Weight Responder (%TBW ≥ 7.5%)	Epitomee®	46	38.7
		Placebo	26	21.5
Week 24 - End of Treatment	Percent change in Total Body Weight Responder (%TBW ≥ 10%)	Epitomee®	32	26.9
		Placebo	13	10.7
Week 24 - End of Treatment	Percent change in Total Body Weight Responder (%TBW ≥ 12.5%)	Epitomee®	20	16.8
		Placebo	8	6.6
* Epitomee® group: N observed =119, N Missing=19 // Placebo group: N observed N=121, N Missing = 20				

Table 13. Difference between groups in responder rate for different "Cutoff" values – FAS

Responder Rate Analysis (Cutoff)	*P* value* difference between groups
Percent change in Total Body Weight Responder (%TBW ≥ 3%)	0.3802
Percent change in Total Body Weight Responder (%TBW ≥ 7.5%)	0.0043
Percent change in Total Body Weight	0.0019

Responder (%TBW ≥ 10%)	
Percent change in Total Body Weight Responder (%TBW ≥ 12.5%)	0.0176
*Logistic regression with baseline weight as covariate	

At Week 24, Epitomee® treatment achieved a greater reduction in Excess Weight Loss (EWL), with an average (SD), of 27.7% (30.3) vs. placebo subjects who lost 21.4% (26.6) (p<0.0043). The mean change (SD) in BMI at week 24 was 2.3-kg/m² (2.3) with Epitomee® vs. 1.6-kg/m² (1.6) with placebo (p=0,0001, FAS, MMRM), resulting in more subjects shifting from Obesity Class II to a lower obesity category. The waist circumference reduction at week 24 was greater with Epitomee® vs. placebo: 6±7cm vs. 5±5.7cm, although the difference was not significant. The extent of reduction in the Epitomee® group was not statistically different from that in the placebo group.

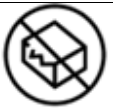
Epitomee® treatment demonstrated improvement in several obesity-related comorbidities. Although the differences between the Epitomee and the control groups were not statistically significant, both systolic (-3.7±12.8 and -2.8±11.7, respectively) and diastolic (-1.5±7.3 and -1.3±8.4, respectively) blood pressure values were statistically improved at week 24 of treatment.

Consistent with the lifestyle intervention program, a within-group reduction (Mean±SD) in Serum insulin (-3.3±13.1 and -1.3±5.9) and triglyceride (-8.4±39.3 and -8.4±28.9) levels at week 24 was significant in both the Epitomee and the Control groups, respectively. However, a significant reduction in FPG (-2.4±10.3) and HOMA IR (-0.9±3.7) , was observed with Epitomee® alone (although the between-group difference was not significant). Furthermore, with Epitomee® a greater number of subjects with prediabetes at baseline reversed to normoglycemic values compared to the placebo.
.
Finally, subjects treated with Epitomee® showed better improvement in quality of life in several items of the IWQOL-Lite-CT questionnaire, as well as the physical function relative to subjects treated with placebo, with physical function score being statistically meaningful and both physical score and total score being marginally significance.

10. EXPLANATION OF SYMBOLS

Medical devices - Symbols to be used with medical device labels, labelling, and information to be supplied

Symbol	Explanation
	Manufacturer
	Medical Device
	Unique Device Identifier
	Authorized representative in the European Community
	Use-By Date

	Catalogue Number
	Batch Code
	Do not use if package is damaged
	Temperature Limit
	Consult instructions for use
	Caution

CE 0476	CE mark
	Country of manufacture
	Importer
	Distributor

	Prescription only
	Single use

 Legal Manufacturer:
Epitomee Medical
17 Hatochen St.
Caesarea 3079892, Israel
www.epitomeemedical.com
info@epitomeemedical.com

KIWA CERMET ITALIA S.P.A.
Via Cadriano, 23, 40057 - Cadriano di Granarolo (BO), Italy
CE 0476

EU Representative:
MedNet EC-REP IIb GmbH,
Borkstrasse 10,
48163 Munster, Germany