DE NOVO CLASSIFICATION REQUEST FOR PLENITY

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Ingested, transient, space occupying device for weight management and/or weight loss. This device is an ingested material that transiently occupies space in the stomach. The device passes from the body via the natural gastrointestinal tract.

NEW REGULATION NUMBER: 21 CFR 876.5982

CLASSIFICATION: Class II

PRODUCT CODE: QFQ

BACKGROUND

DEVICE NAME: Plenity

SUBMISSION NUMBER: DEN180060

DATE DE NOVO RECEIVED: November 15, 2018

SPONSOR INFORMATION:

Gelesis, Inc.
501 Boylston Street, Suite 6102
Boston, MA 02116

INDICATIONS FOR USE

Plenity is indicated to aid in weight management in overweight and obese adults with a Body Mass Index (BMI) of 25 - 40 kg/m^2, when used in conjunction with diet and exercise.

LIMITATIONS

The sale, distribution, and use of Plenity are restricted to prescription use in accordance with 21 CFR 801.109.

In the clinical study of the device, patients were required to use Plenity along with a weight management program of nutrition, diet, and exercise instruction.

Plenity should be taken as directed in the labeling to avoid adverse interaction with other oral medication.

Plenity is contraindicated for use under the following conditions:

- Pregnancy
- History of allergic reaction to cellulose, citric acid, sodium stearyl fumarate, gelatin, or titanium oxide

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

Plenity is a porcine gelatin capsule that contains thousands of absorbent hydrogel particles (0.75 grams [g] per capsule); each particle is approximately the size of a grain of salt (see **Figure 1**). Plenity is non-systemic and works directly in the gastrointestinal (GI) tract. Plenity hydrogel is made from two natural ingredients, cellulose and citric acid, that form a three-dimensional matrix designed to occupy volume in the stomach and small intestine, to create a sensation of fullness. Plenity is provided non-sterile.

Figure 1. Plenity capsules with hydrogel exposed

The capsules disintegrate in the stomach and release the Plenity particles, which can hydrate up to 100 times their original weight. When fully hydrated, the individual non-clustering Plenity particles from the 2.25 g/dose occupy about a quarter of the average stomach volume. The gel particles mix with ingested foods, creating a larger volume with higher elasticity and viscosity in the stomach and small intestine.

Plenity passes through the digestive system, maintaining its three-dimensional structure in the stomach and small intestine before breaking down in the colon. The water is then released and reabsorbed by the body. Plenity particles are eliminated through normal bowel movements; they are not absorbed by the body.

Patients consume three (3) capsules (2.25 g/dose) with water before both lunch and dinner. Plenity is supplied in double blister packs that, together, provide the two doses patients take

daily. Each individual blister pack holds a single dose of three (3) capsules. Seven (7) double blister packs are supplied in a weekly package.

SUMMARY OF NONCLINICAL/BENCH STUDIES

Non-clinical/bench studies conducted on the Plenity device are summarized below.

BIOCOMPATIBILITY/MATERIALS

The Plenity Device is classified as mucosal membrane contacting for repeat, prolonged contact during clinical use (> 24 hours, ≤ 30 days). In accordance with ISO 10993-1, Biological evaluation of medical devices, and FDA Guidance: *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*", the following biocompatibility endpoints were assessed for the Plenity Device:

- Cytotoxicity
- Sensitization
- Irritation
- Oral Irritation
- 7-day Oral Systemic Toxicity
- 90-day Oral Toxicity
- Material-Mediated Pyrogenicity
- Mutagenicty
- Toxicological Risk Assessment

Results support the biocompatibility of the Plenity Device.

PERFORMANCE TESTING - BENCH

The integrity and performance of the Plenity Device was evaluated with the nonclinical testing summarized in **Table 1**

Table 1: Summary of Nonclinical Studies

Test	Purpose	Method	Acceptance Criteria	Results
Nonclinical Performance Testing				
Microbiology testing	Determine device total bioburden and assess for specific enteric and pathogenic microbes to confirm acceptable bioburden	Standard microbiological methods (ISO 4833-2(2013), ISO 21527-2(2008), ISO 16449-2(2010), ISO 6579-1(2008), ISO 6888-3(2004))	Various microbial levels	Pass

Test	Purpose	Method	Acceptance Criteria	Results
Water activity	Determine the relationship between water activity and moisture content	Relative humidity measurements under equilibrium	None	Water activity at (b) (4) moisture content was (b) (4)
Media Uptake Ratio (MUR)	Determine the hydration capacity of the hydrogel particles	Weight of the hydrated hydrogel particles in simulated gastric fluid, minus the weight of the dry hydrogel particles, divided by the weight of the dry hydrogel particles	(b) (4)	(b) (4)
MUR after disintegration	Determine the hydration capacity of the hydrogel particles after gelatin capsule disintegrates	Weight of the hydrated hydrogel particles in simulated gastric fluid, minus the weight of the dry hydrogel particles, divided by the weight of the dry hydrogel particles	(b) (4)	(b) (4)
In vitro simulation of device transit through the GI tract	Ensure that hydrogel particles uptake and release fluid at the correct times during the digestion process	Measure MUR and elastic modulus across time in simulated gastric, intestinal, and colonic fluid	Hydration kinetics and capacity must adequately correlate with GI environment	Results are acceptable
Moisture content determination	Ensure that moisture content does not unnecessarily promote microbial growth	Samples are analytically weighed and then dried at (b) (4) for (b) (4) minutes and then weighed again	(b) (4)	(b) (4)
Elastic modulus	Demonstrate that hydrated hydrogel has comparable mechanical	Swollen particles are put on rheometer plates and tested for	(b) (4)	(b) (4)

Test	Purpose	Method	Acceptance Criteria	Results
	properties to food in the stomach	rheological properties		
Disintegration time	Verify time that it takes for the capsule to disintegrate in the stomach	Capsules are immersed and visually checked at pre-defined time points	Dissolution time ≤ (b) (4) minutes at (b) (4)	Pass
Particle size distribution	Confirm particle dimensions	Testing is conducted by means of analytical sieving	(b) (4) % of particles are between (b) (4) µm (un-hydrated particles)	(b) (4)
Bulk (tapped) density	Support that the correct amount of hydrogel can be encapsulated	Volume of known weight of powder is measured (b) (4)	Hydrogel tapped density (b) (4) mg/ml	(b) (4)
Uniform hydration and disintegration test	Confirm absence of clumps in hydrated material	Hydrate material	Uniform hydration without clumps	Pass
Packaging Integrity Testing				
Package integrity (simulated distribution and shipping followed by associated package integrity testing)	Validate packaging in environmental conditions	Environmental conditioning done in accordance with ASTM F2825:2010 (2015); simulated distribution in accordance with ASTM D4169-16, followed by inspection and bubble emission testing (ASTM D3078-02)	Intact boxes and non-leaking blister packs	Pass
Performance tests on packaged capsules	Ensure that capsules can remain intact and do not prematurely hydrate while in packaging	Pre-determined test methods	Gelatin capsules will visually look unchanged, capsules will disintegrate in no more than (NMT) (b) (4) min, the media ake ratio of the powder in the capsules will be no less than (NLT)	Pass

Test	Purpose	Method	Acceptance Criteria	Results
			(b) (4) the elastic modulus of the powder in the capsules will be NLT (b) (4) the loss of drying of the power in the capsules will be NMT (b) (4)	

SHELF LIFE

Table 2: Summary of Shelf-Life Testing

18-Month Real-Time Shelf-Life Testing				
Media Uptake Ratio (MUR)	Determine the hydration capacity of the hydrogel particles	Weight of the hydrated hydrogel particles in simulated gastric fluid, minus the weight of the dry hydrogel particles, divided by the weight of the dry hydrogel particles	(b) (4)	76.95 ± 0.48 g/g
MUR after disintegration	Determine the hydration capacity of the hydrogel particles after gelatin capsule disintegrates	Weight of the hydrated hydrogel particles in simulated gastric fluid, minus the weight of the dry hydrogel particles, divided by the weight of the dry hydrogel particles	(b) (4)	73.81 ± 0.79 g/g
Moisture content determination	Ensure that moisture content does not promote microbial growth	Moisture loss on drying method	(b) (4) %	(b) (4) %
Elastic modulus	Demonstrate that hydrated hydrogel has comparable mechanical	Swollen particles are put on rheometer plates and tested for	(b) (4) Pa	(b) (4) Pa

	properties to food in the stomach	rheological properties		
Disintegration time	Verify time that it takes for the capsule to disintegrate in the stomach	Capsules are immersed and visually checked at pre-defined time points	Dissolution time ≤ (b) (4) minutes at (b) (4)	Pass
Microbiology testing	Confirm that device is not contaminated with microbial species	Standard microbiological methods	Various microbial levels	Pass
Package integrity (blister pack bubble, leak testing)	Evaluate the packaging integrity to ensure that capsules remain intact and do not prematurely hydrate throughout the shelf-life	Testing done in accordance with ASTM D3078-02 Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission	Seal intact	Pass

SUMMARY OF CLINICAL INFORMATION

Clinical data from a pivotal study (GLOW), small extension study (GLOW-EX), gastric emptying study, and drug-device interaction study were leveraged to evaluate the safety and effectiveness of the Plenity Device.

Pivotal Study (GLOW)

The Gelesis Loss Of Weight (GLOW) trial (ClinicalTrials.gov, NCT02307279) was a multicenter, randomized, double-blind, sham-controlled, parallel-group study assessing the safety and efficacy of 2.25 g of Plenity on body weight over 24 weeks at 33 study sites (US and Europe) in 436 overweight and obese subjects (with and without type 2 diabetes). All subjects were prescribed reduced caloric intake and exercise. Enrollment included subjects ages 22-65 and with BMI 27-40 kg/m^2. Those with BMI <30 kg/m^2 needed to have at least one of the following comorbidities: type 2 diabetes, dyslipidemia, or hypertension. Fasting glucose was required to be between ≥90 mg/dL and ≤145 mg/dL (≥5.0 mmol/L and ≤8.1 mmol/L). The sham used in this study was a placebo consisting of capsules filled with raw cane sugar.

Endpoints

The intent-to-treat (ITT) population is the set of all randomized subjects. The ITT-multiple imputation (ITT-MI) population was the primary group analyzed for primary and secondary endpoints and includes all randomized subjects with multiple imputation performed for missing primary and secondary endpoint data. The ITT-observed (ITT-Obs) population is the set of all randomized subjects who completed the study. The ITT-Obs population was used to analyze the tertiary endpoints. The per protocol (PP) population is the ITT-Obs population but excludes subjects with major protocol deviations or < 80% compliance with taking the dispensed Plenity capsules.

Primary endpoints

The co-primary effectiveness endpoints looked at the change in body weight from baseline to Day 171 (week 25).

- Superiority margin of 3% of the percent total body weight loss (%TBWL) for the Plenity group compared to the Sham group

- More than 35% of subjects on Plenity achieving at least 5% TBWL (performance goal)

Secondary endpoints

- Body weight in subjects with impaired plasma glucose status at baseline (percent change from baseline to Day 171);
- Plasma glucose status (normal, impaired, diabetic) in subjects with impaired plasma glucose status at baseline (change from baseline to Day 171);
- Plasma glucose in subjects with impaired plasma glucose status at baseline and T2D (percent change from baseline to Day 171);
- BMI (change from Baseline to Day 171); and
- HbA1c in subjects with T2D (change from baseline to Day 171).

Assessed Tertiary endpoints

- Body weight responders (≥ 10% weight loss from baseline to Day 171);
- Estimated excess body weight (percent change from baseline to Day 171);
- Waist circumference (change from baseline to Day 171);
- Serum insulin (percent change from baseline to Day 171);
- Homeostasis model assessment-insulin resistance (HOMA-IR) (percent change from baseline to Day 171);
- Serum C-reactive protein (CRP) (change from baseline to Day 171);
- Serum TC (percent change from baseline to Day 171);
- Serum LDL-C (percent change from baseline to Day 171);
- Serum high-density lipoprotein-cholesterol (HDL-C) (percent change from baseline to Day 171);
- Serum TC/HDL-C ratio (change from baseline to Day 171);
- Serum TG (percent change from baseline to Day 171);
- Supine and standing SBP and DBP (change from baseline to Day 171);
- Satisfaction (overall impression on Day 169); and
- Impact of weight on quality of life (IWQOL) (change from baseline to Day 171) at selected sites.

Safety endpoint

- All Adverse Events (AEs) and Serious AEs (SAEs), including Adverse Device Effects (ADEs) and Serious ADEs (SADEs)

To assess safety, the following were conducted or measured:

- Full physical examination (excluding pelvic and rectal examination)
- Supine and standing SBP and DBP

- Supine and standing heart rate
- Hematology including hemoglobin, hematocrit, red blood cell count, reticulocyte count, white blood cell count with differential, and platelet count
- Blood chemistry including plasma glucose and serum sodium, potassium, chloride, calcium, phosphorous, magnesium, blood urea nitrogen, creatinine, uric acid, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, and gamma glutamyltransferase

Study population demographics
The majority of subjects were Caucasian (369 [84.6%] subjects), obese Class I (BMI 30.0 - 34.9 kg/m^2; 237 [54.3%] subjects), middle aged (48.0 ± 10.4 years, mean ± SD) and distributed fairly equally across gender (245 [56.2%] females, 191 [43.8%] males). Dyslipidemia was the most common co-morbidity (69.1% of subjects in the Plenity group; 72.3% of subjects in the Sham group). Most subjects had normal fasting plasma glucose (FPG) at baseline, some were classified as prediabetic (66 [29.6%] subjects in the Plenity group; 66 [31.0%] subjects in the Sham group), and few had type 2 diabetes (T2D) (21 [9.4%] subjects in the Plenity group; 25 [11.7%] subjects in the Sham group).

Subject disposition
A total of 904 subjects were screened in the GLOW study. Of these subjects, 436 were randomized with 223 subjects assigned to the Plenity group and 213 subjects assigned to Sham (intent-to-treat (ITT) cohort). 112 subjects failed to complete the treatment phase citing personal reasons as the most common cause for withdrawal (51 [23%] subjects in the Plenity group and 61 [29%] subjects on Sham). A total of 15 out of 436 (1.1%) subjects withdrew from the study due to adverse events (8 out of 223 [3.6%] subjects in the Plenity group and 7 out of 213 [3.3%] subjects on Sham). A total of 56 out of 436 (12.8%) subjects withdrew from the study based on lifestyle reasons or other personal choices (22 out of 223 [9.9%] subjects in the Plenity group and 34 out of 213 [16%] subjects on Sham). A total of 324 subjects (172 Plenity and 152 Sham) completed the entire treatment phase.

Safety results
Subjects who received treatment after randomization were included in the analysis of safety (n = 223 for Plenity and n = 211 for Sham). Overall, there were 540 (64.3%) mild AEs (282 in 124 [55.6%] subjects in the Plenity group and 258 in 117 [55.5%] subjects in the Sham group) and 276 (32.8%) moderate AEs (143 in 88 [39.5%] subjects in the Plenity group and 133 in 83 [39.3%] subjects in the Sham group) (**Table 3**). The overall incidence of treatment-emergent adverse events in the Plenity treatment group was no different than Sham (71.3% versus 70.6%, respectively) (**Table 4**). In both groups, most (>95%) adverse events were assessed by the investigator as mild or moderate in intensity (**Table 5**). There were no serious adverse events (SAE) in the Plenity group, whereas there was one (1) non-device related SAE in the Sham group (colon adenoma). There were two cases of severe abdominal distension and severe nausea for which discontinuation of the device resulted in resolution. No deaths occurred during the trial.

Table 3: Summary of adverse events by treatment group – Safety Population

	Plenity (N=223)		Sham (N=211)	
	Number Events	**Number Subjects with Event [% (n/N)]**	**Number Events**	**Number Subjects with Event [% (n/N)]**
Number of Subjects with any AE	436	71.3% (159/223)	404	70.6% (149/211)
Grade 3 (Severe)	11	3.6% (8/223)	13	4.7% (10/211)
Grade 2 (Moderate)	143	39.5% (88/223)	133	39.3% (83/211)
Grade 1 (Mild)	282	55.6% (124/223)	258	55.5% (117/211)
Number of Subjects with any SAE	0	0.0% (0/223)	1	0.5% (1/211)
Number of Subjects with AEs leading to withdrawal	29	3.6% (8/223)	21	3.3% (7/211)
Death	0	0.0% (0/223)	0	0.0% (0/211)

Table 4: Summary of Treatment-Emergent Adverse Events by Severity (≥5% by SOC in Either Treatment Group) by Preferred Term, and Severity–Safety Population

	Plenity (N=223)		Sham (N=211)	
	Number Events	**Number Subjects with Event [% (n/N)]**	**Number Events**	**Number Subjects with Event [% (n/N)]**
All Adverse Events	436	71.3% (159/223)	404	70.6% (149/211)
Gastrointestinal disorders				
Abdominal distension	27	11.7% (26/223)	14	6.6% (14/211)
Mild	20	8.5% (19/223)	12	5.7% (12/211)
Moderate	6	2.7% (6/223)	2	0.9% (2/211)
Severe	1	0.4% (1/223)	0	0.0% (0/211)
Abdominal pain	12	5.4% (12/223)	6	2.8% (6/211)
Mild	8	3.6% (8/223)	5	2.4% (5/211)
Moderate	4	1.8% (4/223)	1	0.5% (1/211)
Constipation[1]	13	5.4% (12/223)	11	5.2% (11/211)
Mild	10	4.0% (9/223)	6	2.8% (6/211)
Moderate	3	1.3% (3/223)	5	2.4% (5/211)
Diarrhea	31	12.6% (28/223)	20	8.5% (18/211)
Mild	19	7.6% (17/223)	14	6.2% (13/211)

	Plenity (N=223)		Sham (N=211)	
	Number Events	Number Subjects with Event [% (n/N)]	Number Events	Number Subjects with Event [% (n/N)]
Moderate	12	4.9% (11/223)	5	1.9% (4/211)
Severe	0	0.0% (0/223)	1	0.5% (1/211)
Flatulence	21	8.5% (19/223)	14	5.2% (11/211)
Mild	19	8.1% (18/223)	14	5.2% (11/211)
Moderate	2	0.4% (1/223)	0	0.0% (0/211)
Infrequent bowel movements[1]	24	9.4% (21/223)	12	4.7% (10/211)
Mild	21	8.1% (18/223)	9	3.8% (8/211)
Moderate	3	1.3% (3/223)	3	0.9% (2/211)
Nausea	12	4.9% (11/223)	12	5.2% (11/211)
Mild	8	3.6% (8/223)	9	3.8% (8/211)
Moderate	3	0.9% (2/223)	2	0.9% (2/211)
Severe	1	0.4% (1/223)	1	0.5% (1/211)
Infections and infestations				
Nasopharyngitis	31	11.7% (26/223)	37	14.2% (30/211)
Mild	25	9.0% (20/223)	30	10.9% (23/211)
Moderate	6	2.7% (6/223)	7	3.3% (7/211)
Upper respiratory tract infection	9	3.6% (8/223)	14	5.7% (12/211)
Mild	8	3.1% (7/223)	14	5.7% (12/211)
Moderate	1	0.4% (1/223)	0	0.0% (0/211)
Musculoskeletal and connective tissue disorders				
Arthralgia	9	3.1% (7/223)	13	6.2% (13/211)
Mild	6	2.2% (5/223)	4	1.9% (4/211)
Moderate	3	0.9% (2/223)	7	3.3% (7/211)
Severe	0	0.0% (0/223)	2	0.9% (2/211)
Nervous system disorders				
Headache	23	7.2% (16/223)	26	8.5% (18/211)
Mild	19	5.4% (12/223)	12	3.8% (8/211)
Moderate	3	1.3% (3/223)	12	3.8% (8/211)
Severe	1	0.4% (1/223)	2	0.9% (2/211)
[1] Coded by investigator verbatim terms using Medical Dictionary for Regulatory Authorities [MedDRA] version 17.1				

Table 5: Summary of Gastrointestinal AEs by Severity Deemed Possibly or Most Probably Related to Investigational Product – Safety Population

	Plenity (N=223)		Sham (N=211_	
	Number Events	Number Subjects with Event [% (n/N)]	Number Events	Number Subjects with Event [% (n/N)]
Gastrointestinal Disorders [1]	158	37.7% (84/223)	105	27.5% (58/211)
Mild	119	28.3% (63/223)	83	20.4% (43/211)
Moderate	35	8.1% (18/223)	20	6.6% (14/211)
Severe	4	1.3% (3/223)	2	0.5% (1/211)
[1] Subjects with more than one AE are counted only once, at the worst severity.				

A sub-analysis at four study sites measured vitamin A, B1, B2, B12, B6, B9, D, and E levels at baseline, Day 85, and Day 171. No significant differences were noted from baseline measurements or from the Sham group. No significant difference was observed for serum electrolytes or hematocrit in either group. No signals of altered absorption of medications were observed based on thyroid stimulating hormone levels of subjects on thyroid replacement therapy, blood pressure management while on antihypertensives, low density lipoprotein cholesterol (LDL-C) while on lipid lowering agents.

Efficacy results

The mean ± standard deviation (SD) %TBWL measured in kilogram [kg] from baseline to Day 171 for the ITT-MI population were -6.41 ± 5.79 and -4.39 ± 5.52 in the Plenity and Sham study groups, respectively. The adjusted mean ± standard error (SE) of difference in %TBWL from baseline to Day 171 (week 25) was -2.07 ± 0.59 (95% confidence interval (CI): -3.24, -0.90)

The difference did not meet the pre-defined threshold of 3% and the lower limit of the CI did not surpass 3%; therefore, super-superiority had not been established. However, while the difference in weight reduction did not meet the super-superiority threshold, the difference between the Plenity and Sham groups (-6.41 ± 5.79 vs. -4.39 ± 5.52) was statistically different (p = 0.0007). **Table 6** provides the study results for the %TBWL in the ITT-MI and PP study populations. The ITT analyses could be influenced by the choice of statistical models, so the PP population analysis without statistical analysis is presented for transparency purposes.

Table 6: Percent TBWL from baseline to Day 171

ITT-MI Analysis Population	Plenity (N=223)	Sham (N=213)
Percent TBWL [1]		
Mean ± SD	-6.41 ± 5.79	-4.39 ± 5.52
Median (min, max)	-5.80 (-26.40, 7.74)	-3.97 (-22.31, 15.90)
LS Mean Difference [2]		
Mean ± SE	-2.07 ± 0.59	
95% CI [3]	(-3.24, -0.90)	
p-value: Super Superiority [4]	0.1193	

ITT-MI Analysis Population	Plenity (N=223)	Sham (N=213)
p-value: Superiority [5]	0.0007	
PP Analysis Population	**Plenity (N=154)**	**Sham (N=141)**
Percent TBWL		
Mean ± SD	-6.31 ± 6.01	-4.89 ± 5.40
Median (min, max)	-5.73 (-26.40, 7.74)	-4.15 (-19.25, 10.42)
Difference (95% CI)	-1.42 (-2.73, -0.10)	

[1] Endpoint data imputed for 22.9% (51/223) in Plenity group and 28.6% (61/213) in Sham group.
[2] Difference in adjusted means taken for comparability between the two groups.
[3] 95% Confidence Interval for the difference in LS means.
[4] p-value from ANCOVA model adjusted for stratification factors and baseline weight, testing for super superiority (> 3% difference).
[5] p-value from ANCOVA model adjusted for stratification factors and baseline weight, testing for superiority (difference > 0).

Of the 436 randomized subjects, 245 of them were from European study sites and 191 from US study sites. A pooling analysis of the pivotal study was done for treatment difference on the mean of the co-primary endpoint of percent TBWL in the ITT-MI population. The unadjusted difference in treatment mean (treatment – control) and the 95% CI of this difference is -2.39% (-3.94%, -0.84%) and -1.50% (-3.16%, 0.16%) for the European pooled region and the US pooled region respectively.

The co-primary endpoint of body weight responders was successfully achieved. The percent of responders with ≥5% weight loss was 58.6% (95% CI: 51.8, 65.4), significantly exceeding the performance goal of 35% (p<0.0001). **Table 7** provides the study results for responder rates in the ITT-MI and PP study populations. The ITT analyses could be influenced by the choice of statistical models, so the PP population analysis without statistical analysis is presented for transparency purposes.

Table 7: Body Weight Responders ≥ 5% TBWL from baseline to Day 171

ITT-MI Analysis Population	Plenity (N=223)	Sham (N=213)
Percent of body weight responders [1, 2]	58.6	42.2
95% CI	(51.8, 65.3)	(35.2, 49.1)
p-value [3]	<0.0001	
PP Analysis Population	**Plenity (N=154)**	**Sham (N=141)**
Percent of body weight responders [2]	57.1	44.0
95% CI	(48.9, 65.1)	(35.6, 52.6)
p-value [3]	<0.0001	

[1] Endpoint data imputed for 22.9% (51/223) in Plenity group and 28.6% (61/213) in Sham group.
[2] Body weight responders defined as patients with ≥5% reduction in body weight.
[3] p-value from binomial proportion test for % of responders in treatment group compared to 35% performance goal.

A tipping point analysis was conducted for the performance goal of 5% weight loss and the 35% responder analysis. If all 51 missing values in the Plenity group were failures, there would be 100 (44.8%) 5% responders (95% CI: 38.2, 51.6). With all missing values set to failures, the study would have still shown success against the performance goal of 35%.

The first secondary effectiveness endpoint did not achieve statistical significance. Since the first secondary endpoint did not achieve $p<0.05$ significance level all the other secondary endpoints were evaluated only as descriptive statistics. Notably, at the Day 171 assessment, BMI means (SD) in the ITT-MI population were 31.43 (3.66) kg/m^2 and 32.57 (3.72) kg/m^2 for the Plenity and Sham treatment groups, respectively. The mean changes (SD) in BMI from baseline to Day 171 were -2.12 kg/m^2 (1.92) and -1.51 kg/m^2 (1.90) for the Plenity and Sham treatment groups, respectively. The adjusted mean (SE) change in BMI from baseline to Day 171 for the treatment difference for Plenity versus Sham was -0.60 kg/m^2 (0.20) (95% CI; -1.00, -0.20) from an ANCOVA model adjusting for stratification factors and baseline BMI.

The initial statistical testing of the tertiary endpoints did not achieve significance, and therefore all subsequent evaluations were based on descriptive statistics. Multiple prespecified tertiary endpoints were measured in the ITT-Obs population, including 10% total body weight responders, estimated excess body weight loss, and change in waist circumference (**Table 8**). All differences between treatment groups and 95% CI's shown are from analyses adjusting for stratification factors and the corresponding baseline value for the respective endpoint. For 10% body weight responders, the Plenity arm had 26% (45/172) while the Sham arm had 16% (25/152), with the odds of being a 10% responder in the Plenity arm 1.88 (95% CI; 1.07, 3.30) times the odds in the Sham arm. For excess body weight loss, the Plenity arm had -28.96 (30.14) percent change while the Sham arm had -20.98 (25.69) percent change. The patients in the Plenity arm achieved more excess body weight loss than those in the Sham arm, the adjusted difference between groups was -6.44 (2.94) (95% CI; -12.2, -0.64). Similarly, the patients in the Plenity arm achieved greater reduction in waist circumference than those in the Sham arm: -2.64 inches (2.19) and -1.98 inches (2.32), respectively. The adjusted difference in change in waist circumference between the two groups was -0.73 in (0.25) with a 95% CI of (-1.22, -0.24).

Table 8: Tertiary Endpoints for Change or Percent Change from baseline to Day 171 – ITT-Obs Population

Tertiary Endpoints	Plenity (N = 172)	Sham (N = 152)	Difference [1]	95% CI [2]
Estimated excess body weight (% change) Mean ± SD	-28.96 ± 30.14	-20.98 ± 25.69	-6.44 ± 2.94	(-12.23, -0.64)
Waist circumference (change in inches) Mean ± SD	-2.64 ± 2.19	-1.98 ± 2.32	-0.73 ± 0.25	(-1.22, -0.24)

[1] Difference in adjusted means taken for comparability between the two groups (T - C)
[2] 95% Confidence Interval for the difference in LS means.

Patient perspectives considered for the Plenity during the review were GLOW study tertiary endpoints of subject satisfaction and Impact of Weight on Quality of Life (IWQOL). Measured satisfaction levels were increased from baseline and comparable between the treatment and control study arms.

Extended Study (GLOW-EX)

This study assessed the effect of Plenity on body weight after an additional exposure of 24 weeks in subjects in the Plenity and Sham groups who completed the 24-week treatment period of the GLOW study and had at least 3% weight loss. Measurements were made on Day 339 from baseline (~48 weeks). This is an open-label, one arm extension study and all subjects were treated with Plenity 2.25 g, twice daily. The GLOW-EX study was conducted at 15 clinical sites in 5 countries in the US and Europe. Of the 15 clinical sites, 11 enrolled subjects into the study.

The following study groups were assessed:

- active-active (subjects who received Plenity in the GLOW study)
- control-active (subjects who received the Sham in the GLOW study)

Of the 324 subjects who completed the treatment phase of the GLOW study, 18 subjects who were assigned to Sham and 21 subjects who were assigned to Plenity were enrolled in GLOW-EX. Of these, 17 and 18 subjects, respectively, completed the extended treatment of the study.

Endpoints

Co-primary endpoints:

- Body weight (percent change from baseline of the GLOW study to Day 339)
- Body weight (percent change from baseline of the GLOW-EX study to Day 339)
- Body weight responders (≥ 5% weight loss from baseline of the GLOW study to Day 339)
- Body weight responders (≥ 5% weight loss from baseline of the GLOW-EX study to Day 339)

Assessed Secondary endpoints

- Plasma glucose (percent change from baseline of the GLOW study to Day 339)
- Plasma glucose (percent change from baseline of the GLOW-EX study to Day 339)
- HOMA-IR (percent change from baseline of the GLOW study to Day 339)
- HOMA-IR (percent change from baseline of the GLOW-EX study to Day 339)
- Body mass index (BMI) (change from baseline of the GLOW study to Day 339)
- BMI (change from baseline of the GLOW-EX study to Day 339)

Assessed Tertiary endpoints

- Body weight responders (≥ 10% weight loss from baseline of the GLOW study to Day 339)
- Body weight responders (≥ 10% weight loss from baseline of the GLOW-EX study to Day 339)
- Estimated excess body weight (percent change from baseline of the GLOW study to Day 339)
- Estimated excess body weight (percent change from baseline of the GLOW-EX study to Day 339)
- Waist circumference (change from baseline of the GLOW study to Day 339)
- Waist circumference (change from baseline of the GLOW-EX study to Day 339)

Safety endpoint

- All AEs and SAEs (including ADEs and SADEs)

To assess safety, the following were conducted or measured:

- Full physical examination (excluding pelvic and rectal examination)
- Supine and standing SBP and DBP
- Supine and standing heart rate
- Hematology including hemoglobin, hematocrit, red blood cell count, reticulocyte count, white blood cell count with differential, and platelet count
- Blood chemistry including plasma glucose and serum sodium, potassium, chloride, calcium, phosphorous, magnesium, blood urea nitrogen, creatinine, uric acid, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, and gamma glutamyltransferase

Safety results

Adverse events in the last 24 weeks (GLOW-EX) were compared to the first 24 weeks (GLOW study) for the overall safety population (n = 223) and for the GLOW-EX subjects only.

The overall incidence of AEs was no different between the Plenity subjects who were exposed for an entire year (29 AEs in 10 [47.6%] subjects) versus the Sham subjects who were switched to Plenity and exposed to Plenity for the first time for a period of 24 weeks (37 AEs in 12 [66.7%] subjects). There were 11/29 AEs in 4 (19.0%) subjects deemed related (Possibly or Most Probably) to Plenity. Most of these were mild gastrointestinal (GI) events which were similar to what was observed in the first 24 weeks (GLOW study). There were no deaths and no SAEs.

The most common AEs (based on MedDRA's version 17.1) in descending order of frequency for the Plenity-Plenity group during GLOW-EX were:

- Infrequent bowel movements: 5 AEs in 3 (14.3%) subjects;
- Headache: 4 AEs in 3 (14.3%) subjects;
- Abdominal distension: 2 AEs in 2 (9.5%) subjects; and
- Constipation: 2 AEs in 2 (9.5%) subjects.

The most common AEs (based on MedDRA's version 17.1) in descending order of frequency in the Sham-Plenity group during GLOW-EX were:

- Nausea: 3 AEs in 2 (11.1%) subjects;
- Headache: 2 AEs in 2 (11.1%) subjects;
- Nasopharyngitis: 2 AEs in 2 (11.1%) subjects; and
- Oropharyngeal pain: 2 AEs in 2 (11.1%) subjects.

Efficacy results

At the time of enrollment in GLOW-EX, the subjects treated with Plenity during GLOW (21 subjects) had already reached a mean ± SD %TBWL of 7.1% ± 2.8%. The additional six (6) months of exposure to Plenity provided an additional 0.8 ± 3.0% weight loss for a total of 7.9%

weight loss after 48 weeks. At entry in the GLOW-EX extension study, 15 of these 21 subjects had reached at least 5% weight loss, and, among that subset, 12 out of 15 maintained that weight threshold over the following 6 months. All 5 of the 21 subjects who had achieved the 10% threshold by entry into the GLOW-EX extension study maintained that threshold through 1 year with continuation of Plenity. The primary endpoint of weight maintenance with continuation of Plenity was demonstrated as the 95% confidence intervals at day 171 (-8.37 to -5.78) and day 339 (-10.54 to -5.22) overlap.

The 18 subjects assigned to Sham in GLOW had already reached a mean ± SD %TBWL of 7.1% ± 4.1% during the GLOW study before starting on Plenity for 24 weeks. These subjects, who successfully lost with lifestyle modification, were able to lose an additional 2.5% ± 4.1% over the subsequent 24 weeks with the addition of Plenity. At entry in the GLOW-EX extension study, 11 of the 18 subjects had reached at least 5% weight loss, and, among that subset, 10 out of these 11 subjects maintained their 5% TBWL status in the subsequent 24 weeks.

Gastric Emptying Study (IMAGES)

The IMAGES Study was a single center partially-blinded, randomized, four-way, crossover, two-part study involving eight overweight/obese male volunteers in each part designed to assess and compare the gastric emptying kinetics and gastrointestinal (GI) transit times of a radiolabeled meal following a single administration of either 2.25g or 3.75g of Plenity or Sham.

No differences were observed in the rate of gastric emptying between Plenity and Sham arms of the study.

Drug-Device Interaction Study

A drug-device interaction study was conducted to evaluate the effect of Plenity capsules on the pharmacokinetics (PK) of metformin, administered as single dose in healthy, overweight or obese subjects (N=24). This was a single center, randomized, single-dose, open-label, 4-period, 4-way, crossover, device-drug interaction, performed under fasting and fed conditions.

Results support that Plenity affects metformin absorption similar to food. Plenity should be administered as directed under the directions for use.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The labeling comprises patient and physician labeling that includes the device indications for use, a description of the device, warnings and precautions, clinical data on the device, and instructions for the safe and effective use of the device. The labeling satisfies the requirements of 21 CFR 801.109 Prescription devices.

Per the Special Controls for this generic type of device, labeling includes the following:

- Safety instructions intended to minimize the risks of improper device use, including when to take the device with medication

- Contraindications and warnings to ensure usage of the device for the intended patient population

- A detailed summary of the clinical testing including device effectiveness and device related adverse events and a summary of baseline demographic information

- A shelf life for the device.

RISKS TO HEALTH

The table below (**Table 9**) identifies the risks to health that may be associated with use of an ingested, transient, space occupying device for weight management and/or weight loss, and the measures necessary to mitigate these risks.

Table 9: Identified Risks to Health and Mitigation Measures

Identified Risks to Health	**Mitigation Measures**
Device related gastrointestinal adverse events, including: • Obstruction • Dilation • Diarrhea • Constipation • Dehydration	Clinical performance testing Non-clinical performance testing Labeling Shelf life testing
Weight gain	Clinical performance testing Labeling
Interaction with medication	Clinical performance testing Non-clinical performance testing Labeling
Adverse tissue reaction	Biocompatibility evaluation
Infection	Non-clinical performance testing Shelf life testing

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the ingested, transient, space occupying device for weight management and/or weight loss is subject to the following special controls:

(1) The patient-contacting components of the device must be demonstrated to be biocompatible for its intended use.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions for use, as follows:

(i) Performance bench testing in a simulated use model must evaluate device disintegration and device hydration state throughout the gastrointestinal tract.

(ii) Bioburden and moisture content assessments must evaluate device infection risk throughout the labeled shelf life.

(iii) Performance data must support the shelf life of the device by demonstrating continued package integrity and device functionality over the labeled shelf life.

(3) Clinical performance testing must demonstrate the device performs as intended and evaluate the following:

(i) Weight change;

(ii) All adverse events, including obstruction, dilation, diarrhea, constipation, and dehydration; and

(iii) Interaction with representative medications.

(4) Physician and patient device labeling must state:

(i) The clinical benefit of the device as assessed by using percent total body weight loss;

(ii) Treatment must be offered in combination with diet and exercise;

(iii) Instructions on how to use the device as intended including how to avoid interaction with medication; and

(iv) The shelf life of the device.

BENEFIT-RISK DETERMINATION

The risks of the device are based on nonclinical laboratory studies as well as data collected in the clinical studies described above.

The overall incidence of adverse events in the pivotal clinical study (GLOW) in the Plenity treatment group was not different than Sham (71.3% versus 70.6%, respectively). The majority of the events were mild in nature. Only 3.6% of the events were considered severe, 39.5 % were moderate, and 55.6% were mild. There were slightly higher rates of GI-related AEs in the Plenity treatment arm relative to the Sham arm. The majority of GI AEs (37.7%) were device-related. The AEs were diarrhea, abdominal distension, flatulence, constipation, abdominal pain and nausea. This is expected for this device type. There were no serious adverse events (SAEs) or

deaths. There were, however, two cases of severe abdominal distension and severe nausea for which discontinuation of the device resulted in resolution. In the extended clinical study (GLOW-EX), the overall incidence of AEs was no different between the Plenity subjects who were exposed for an entire year (29 AEs in 10 [47.6%] subjects) versus the Sham subjects who had sham capsules for 24 weeks, and then Plenity for 24 weeks (37 AEs in 12 [66.7%] subjects).

The GLOW pivotal clinical study showed minimal weight loss with 2.25 g of Plenity daily relative to Sham therapy (sugar filled capsules) in patients who used the device for 171 days. Subjects taking Plenity lost on average 6.4% TBWL vs 4.4% TBWL in subject taking the Sham sugar pill. Although the co-primary endpoint of a 3% TBWL superiority margin was not met, there was statistically significant greater %TBWL in the treated group versus the control group. The co-primary endpoint of percent responders with ≥ 5% TBWL was 58.6% with Plenity vs 42.2% with Sham and was of statistical significance. There were secondary and tertiary endpoint analyses in the pivotal clinical study that showed some benefit of Plenity use.

An extended study (GLOW-EX) assessed the effect of Plenity on body weight after an additional exposure of 24 weeks in subjects who completed the 24-week treatment period of the GLOW study and had at least 3% TBWL (48 weeks total device exposure). Twenty-one (21) subjects taking Plenity kept taking Plenity, and 18 subjects taking Sham took Plenity during this extended study. Weight loss was assessed at 48 weeks (339 days) post baseline of the GLOW study.

The GLOW-EX enrolled subjects treated with Plenity had reached a mean ± SD %TBWL of 7.1% ± 2.8% at the end of the GLOW study. These subjects maintained that loss ending with 7.9% TBWL. The 18 subjects assigned to Sham in GLOW had lost 7.1% ± 4.1% TBWL during the GLOW study before starting on Plenity for 24 weeks. The subjects who successfully lost with lifestyle modification were able to lose an additional 2.5% ± 4.1% TBWL over the subsequent 24 weeks with the addition of Plenity.

There are several items that lead to uncertainty about the applicability of the study results across the broad US patient population: treatment withdrawal rate, diversity of study subjects, non-US subjects.

- The treatment withdrawal rate was 23% (51/223) for the Plenity arm and 29% (61/213) for the Sham arm of the study. The large amount of missing data made the primary ITT analysis more dependent on the statistical models used.

- The baseline parameters were appropriately balanced between the Plenity arm and the Sham arm; however, there was a bias toward Caucasian subjects with rates: 84.8% white, 11.7% African-American, and 4.9% Hispanic. The study population may not represent the patient population who are obese or overweight in the US.

- Of the 436 randomized subjects, 245 of them were from European study sites and 191 from US study sites. A pooling analysis of the pivotal study was done for treatment difference on the mean of the co-primary endpoint of percent TBWL in the ITT-MI population. The unadjusted difference in treatment mean (treatment – control) and the 95% CI of this difference is -2.39% (-3.94%, -0.84%) and -1.50% (-3.16%, 0.16%) for

the European pooled region and the US pooled region, respectively. Thus, patients in the US may see less benefit from the use of Plenity than may European patients.

The level of effectiveness of the Plenity device demonstrated through clinical studies is not appropriate for an indication of weight loss. However, the Plenity device has demonstrated effectiveness when used as an aid to weight management.

Patient Perspectives

Patient perspectives considered for the Plenity during the review were GLOW study tertiary endpoints of subject satisfaction and Impact of Weight on Quality of Life (IWQOL). Measured satisfaction levels were increased from baseline and comparable between the treatment and control study arms.

Benefit/Risk Conclusion

In the clinical study, one of the co-primary endpoints was met, demonstrating a modest clinical benefit in weight loss. There is moderate uncertainty in the benefit. However, considering the very low adverse event profile, the low level of uncertainty associated with the risks of the device, and the fact that the overall incidence of adverse events in the Plenity group were similar to the Sham group, the benefit-risk profile is favorable.

In conclusion, given the available information above, for the following indication statement:

> Plenity is indicated to aid in weight management in overweight and obese adults with a Body Mass Index (BMI) of 25 – 40 kg/m^2, when used in conjunction with diet and exercise

the probable benefits outweigh the probable risks for the Plenity. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for Plenity is granted and the device is classified as follows:

> Product Code: QFQ
> Device Type: Ingested, transient, space occupying device for weight management and/or weight loss
> Regulation Number: 21 CFR 876.5982
> Class: II