CLINICAL INVESTIGATION PLAN (PROTOCOL)

PRODUCT: Gelesis100

TITLE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Assessing the Effect of Gelesis100 on Body Weight in Overweight and Obese Subjects with and without Type 2 Diabetes

STUDY NAME: GLOW (Gelesis Loss Of Weight)

PROTOCOL NUMBER: G-04

VERSION: 5.0 (Post-Amendment 4)

VERSION DATE: August 24, 2016 (Final)

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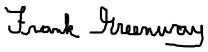
PRINCIPAL/COORDINATING INVESTIGATOR EMERGENCY CONTACT BACKUP	Name: Frank L. Greenway, M.D. Address: Pennington Biomedical Research Center 6400 Perkins Road Baton Rouge, LA 70808 USA Phone: +1 225 763-2578 Fax: +1 225 763-3022 E-mail: frank.greenway@pbrc.edu Signature: 

CHANGES

Replacement:
- Page 3 (Principal/Coordinator Investigator)

Addition:
- Section 1 (Body weight criteria, Interim analysis)
- Section 2 (Serum amylase, Genomic tests, Procedures for extension study)
- Section 4 (AMY1, BDNF, CAPN10, CP, FTO, KCNJ11, LEPR, MC4R, NEGR1, NPC1, PCSK1, PPARG, SH2B1, SLC16A13, TCF7L2)
- Section 5.2 (Details on hydration of Gelesis100)
- Section 7 (Description of extension study)
- Section 8.1 (Serum lipids)
- Section 8.3 (Body weight criteria)
- Section 11.3 (Physical activity)
- Section 11.3.2.1 (Serum amylase, Genomic tests)
- Section 12.1 (Scheduling of Visit 2 and Visit 13)
- Section 12.2.1 (Serum amylase, Genomic tests)
- Section 12.2.12 (Informed consent related to extension study)
- Section 12.2.13 (Randomization related to extension study, Visit status related to extension study)
- Section 15.5.4 (Interim analysis, Management of SADE)
- Section 15.5.4.1 (Unblinding for interim analysis)
- Section 15.5.4.2 (Unblinding for management of SADE)
- Section 15.6 (Interim analysis)
- Section 15.7.5 (Serum amylase, Genomic tests)
- Section 26 (References)

Deletion:
- Section 4 (Ltd., s.r.o.)
- Section 8.2 (Competitive enrollment)
- Section 9.2.1 (Medication for chronic disease)

Clarification and Optimization:
- Section 9.1 (11 mg)
- Section 11.3.1.7 (Mild binge eater)
- Section 13.1.3 (Health Canada)
- Section 13.3.2 (Health Canada)
- Section 14.2.1 (Stopping rules, Interim analysis)
- Section 15.3 (Study endpoints)
- Section 15.4 (Sample size determination)
- Section 15.7 (Statistics)
- Section 15.7.1.1 (ITT population)
- Section 15.8 (Statistics)
- Section 15.8.6.1 (Study endpoints)

- Section 15.8.6.3 (Statistics)
- Section 17.2 (Informed Consent Form)
- Section 18.7 (Financial arrangements)
- Section 20 (Protocol deviations)
- Section 25 (Audit by Sponsor)

Correction:

- Section 9.1.9 (Detailed)
- Section 15.7.3 (Biased)

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1. CLINICAL TRIAL SUMMARY

TITLE	A randomized, double-blind, placebo-controlled, parallel-group study assessing the effect of Gelesis100 on body weight in overweight and obese subjects with and without type 2 diabetes
OBJECTIVES	**Primary:** - placebo-adjusted weight loss ≥ 3.0% - weight loss of at least 5% in ≥ 35% of subjects on Gelesis100 **Secondary:** - decrease in serum insulin - decrease in insulin resistance (homeostasis model assessment-insulin resistance "HOMA-IR") - decrease in plasma glucose - decrease in glycosylated hemoglobin (HbA1c) - safety and tolerability similar to placebo or clinically acceptable
DESIGN	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-amount
NUMBER OF SUBJECTS	Approximately 460: - 230 subjects on Gelesis100 - 230 subjects on placebo
COUNTRIES AND SITES	US, Canada, and several European countries, approximately 38 sites
INCLUSION CRITERIA	- male and female ambulatory subjects (it is recommended to have at least 45% of each gender) - age ≥ 22 years and ≤ 65 years - body mass index (BMI) ≥ 27 and ≤ 40 (it is recommended to have at least 70% of subjects with BMI < 35 and body weight < 120 kg in at least 92% of all subjects; subjects with BMI < 30 should have at least one comorbidity including untreated or

	metformin-treated type 2 diabetes, untreated dyslipidemia with low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL (≥ 3.37 mmol/L) and/or triglycerides ≥ 150 mg/dL (≥ 1.69 mmol/L) or drug-treated dyslipidemia, and untreated hypertension with supine systolic blood pressure (SBP) ≥ 140 mm Hg and/or supine diastolic blood pressure (DBP) ≥ 90 mm Hg based on the mean of two consecutive readings or drug-treated hypertension) - fasting plasma glucose ≥ 90 mg/dL and ≤ 145 mg/dL (≥ 5.0 mmol/L and ≤ 8.1 mmol/L); it is recommended to have approximately 45 to 55% non-diabetic normoglycemic subjects (fasting glucose ≥ 90 mg/dL and < 100 mg/dL or ≥ 5.0 mmol/L and < 5.6 mmol/L) and the rest, non-diabetic impaired fasting glucose subjects (fasting glucose ≥ 100 mg/dL and < 126 mg/dL or ≥ 5.6 mmol/L and < 7.0 mmol/L) or diabetic subjects either untreated (fasting glucose ≥ 126 mg/dL and ≤ 145 mg/dL or ≥ 7.0 mmol/L and ≤ 8.1 mmol/L) or metformin-treated (metformin dose ≤ 1500 mg/day, fasting glucose ≤ 145 mg/dL or ≤ 8.1 mmol/L) - ability to follow verbal and written instructions - informed consent form signed by the subjects
EXCLUSION CRITERIA	- pregnancy (or positive serum or urine pregnancy test(s) in females of childbearing potential) or lactation - absence of contraception in females of childbearing potential - history of allergic reaction to carboxymethylcellulose, citric acid, sodium stearyl fumarate, raw cane sugar, gelatin, and titanium dioxide - administration of investigational products within 1 month prior to Screening Visit - subjects who stopped smoking within 6 months prior to Screening Visit or considering smoking cessation during the

	study - subjects anticipating surgical intervention during the study - known type 1 diabetes - history of eating disorders including binge eating (except mild binge eater) - weight change > 3 kg within 3 months prior to and during the Screening period - supine SBP > 160 mm Hg and/or supine DBP > 95 mm Hg - angina, coronary bypass, or myocardial infarction within 6 months prior to Screening Visit - history of swallowing disorders - esophageal anatomic abnormalities (e.g., webs, diverticuli, rings) - history of gastroesophageal reflux disease - history of gastric or duodenal ulcer - history of gastroparesis (chronic nausea, vomiting, heartburn, …) - history of gastric bypass or any other gastric surgery - history of small bowel resection (except if related to appendectomy) - history of intestinal stricture (e.g., Crohn's disease) - history of intestinal obstruction or subjects at high risk of intestinal obstruction including suspected small bowel adhesions - history of abdominal radiation treatment - history of pancreatitis - history of malabsorption - history of sucrose intolerance - laxative users - history of hepatitis B or C - history of human immunodeficiency virus - history of cancer within the past 5 years (except adequately-treated localized basal cell skin cancer or *in situ* uterine cervical cancer) - any other clinically significant disease interfering with the assessments of Gelesis100 (e.g., disease requiring corrective treatment, potentially leading to study discontinuation) - abnormal serum thyroid-stimulating hormone (TSH)

	- HbA1c > 8.5% (> 69 mmol/mol) - serum LDL cholesterol ≥ 190 mg/dL (≥ 4.93 mmol/L) - serum triglycerides ≥ 500 mg/dL (≥ 5.65 mmol/L) - positive test for drugs in the urine - any relevant biochemical abnormality interfering with the assessments of Gelesis100 - anti-obesity medications (including herbal preparations) within 1 month prior to Screening Visit - antidiabetic medications within 1 month prior to Screening Visit (except stable dose of metformin, ≤ 1500 mg/day, for at least 1 month in subjects with type 2 diabetes) - systemic corticosteroids within 1 month prior to Screening Visit - thyroid hormones or preparations within 1 month prior to Screening Visit (except stable dose of replacement therapy for at least 1 month) - TSH suppression therapy for thyroid cancer - estrogen within 1 month prior to Screening Visit (except stable dose of replacement therapy for at least 1 month or non-oral contraceptive for at least 3 months) - any other medication or product known to cause weight loss or weight gain within 1 month prior to Screening Visit - change in medications treating dyslipidemia within 1 month prior to Screening Visit (including change in dose) - change in medications treating hypertension within 1 month prior to Screening Visit (including change in dose) - medications requiring mandatory administration with meal at lunch or dinner - anticipated requirement for use of prohibited concomitant medications
INVESTIGATIONAL PRODUCT	Gelesis100 (medical device in capsule) and matching placebo
TREATMENT ASSIGNMENT	Gelesis100 (2.25 g) versus placebo, twice daily, before lunch and dinner (20-30 min

AND ADMINISTRATION	before meal) Randomization ratio of 1:1 with 230 subjects per arm (2 arms) Stratification by country (or combination of countries), based on gender (male and female), BMI at Screening Visit (< 35 and ≥ 35), and fasting glucose status at Screening Visit (normal and impaired/diabetic) Subjects to be treated in a parallel-group design, for 24 weeks
DIET AND LIFE-STYLE	- hypocaloric diet (-300 kcal/day), meals to be consumed with water as instructed - moderate-intensity exercise - no change in smoking habits
STUDY DURATION PER SUBJECT	**Screening period:** up to 3 weeks **Baseline period:** 1 day **Treatment period:** 24 weeks **Post-treatment follow-up period:** 4 weeks
TOTAL STUDY DURATION	Approximately 2 years (including approximately 1 and half years for enrollment)
EFFECTIVENESS ENDPOINTS	**Co-primary:** - body weight - body weight responders (≥ 5% weight loss) **Secondary:** - plasma glucose status - plasma glucose - HOMA-IR - HbA1c - BMI **Tertiary:** - body weight responders (≥ 10% weight loss) - estimated excess body weight - body weight status - waist circumference - serum insulin

	- serum C-reactive protein (CRP) - serum lipids - blood pressure - food intake - food habits - satisfaction - impact of weight on quality of life (IWQOL)
SAFETY ENDPOINTS	- adverse events (AEs) - physical examination - vital signs - laboratory tests
VISITS	Fourteen visits including the Screening Visit
STATISTICAL ANALYSIS	- this sample size of 460 randomized subjects (230 per arm) with an anticipated dropout rate of 30% (322 subjects completing the study, 161 per arm) will allow establishing both super-superiority and superiority with sufficient statistical power - the sample size will provide 85% statistical power for a 3.0% margin super-superiority (i.e., delta of at least 4.5%) with a common SD of 5.0% and a type I error rate of 0.05 (one-sided test) - the sample size will also provide at least 90% statistical power to establish the superiority (difference between the two arms greater than 0) with a common SD of 5.0% and a type I error rate of 0.05 (two-sided tests) - study endpoints will be analyzed as percent change or change from baseline to Days 169 or 171 - continuous parameters will be assessed by analysis of covariance model using the stratification factors and the respective baseline values for the endpoint in the model - categorical parameters will be assessed by Logit model using the stratification factors and the respective baseline values for the endpoint in the model - safety data will be summarized for each arm

	- an interim analysis will be performed when approximately 50% of subjects have been randomized and completed Visit 13 (Week 24) or early terminated, whichever comes first
STUDY START DATE	Second half of 2014
STUDY END DATE	First half of 2017

2. STUDY FLOW CHART

Period (duration)	**Screening (≤ 21 days)**	**Baseline (1 day)**	**Double-blind treatment (168 days)**										**Follow-up (28 days)**	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13[I]	14
Day	-21 to -1	0	8	15	29	43	57	71	85	113	141	169	171	197
Week	-3 to 0	0	1	2	4	6	8	10	12	16	20	24	25	28
Informed consent	X												X[J]	
Demography, height	X													
Menopausal status, smoking status, medical history	X													
Physical examination	X	X							X				X	
Weight, waist circumference, vital signs (blood pressure, heart rate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary interview	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Binge eating disorder	X													
Food habits before treatment		X												
Serum pregnancy test[A]	X	X							X				X	
Urine pregnancy test[A], serum amylase[B], genomic tests[C]		X												
Electrocardiogram, urine drug screen	X													
TSH[D]	X								X					
Plasma glucose	X	X	X	X	X				X				X	
Serum insulin		X	X	X	X				X				X	
IWQOL[E]		X											X	
Serum CRP, vitamins[F]		X							X				X	
Serum albumin	X	X		X	X				X				X	
Hematology, blood chemistry, HbA1c	X	X							X				X	
Food intake[G]		X			X		X		X	X	X	X		
Food habits and satisfaction after treatment												X		
Concomitant medication recording, AEs recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X												
Gelesis100/placebo accountability			X	X	X	X	X	X	X	X	X	X		
Gelesis100/placebo dispensed[H]		X	X	X	X	X	X	X	X	X	X			

[A]Females of childbearing potential only. [B]At any of the Visits 2, 3, 4, 5, 9, or 13. [C]At any of the Visits 2, 3, 4, 5, 9, or 13 (tests not mandatory). [D]The assessment of Week 12 is for subjects on replacement therapy with thyroid hormones or preparations only. [E]At selected sites. [F]At selected sites (vitamins include vitamin A, vitamins B_1, B_2, B_6, B_9, and B_{12}, vitamin D, and vitamin E). [G]Food diary on 2 consecutive weekdays and 1 weekend day before the visit. [H]Administration begins on Day 1 and continues through Day 168, before lunch and dinner. [I]Last visit if entering extension study. [J]If entering extension study.

3. CLINICAL INVESTIGATION PLAN APPROVAL

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Assessing the Effect of Gelesis100 on Body Weight in Overweight and Obese Subjects with and without Type 2 Diabetes.

I agree to the terms of this Clinical Investigation Plan. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practices, ISO 14155:2011, and local regulations and requirements.

Investigator:

Name: _____

Signature: _____

Date: _____

4. ABBREVIATIONS

ADE: adverse device effect
AE: adverse event
am: ante meridiem
AMY1: salivary amylase
ANCOVA: analysis of covariance
BDNF: brain-derived neurotrophic factor
BMI: body mass index
C: Celsius
CAPN10: calpain-10
CEE: Central and Eastern Europe
cm: centimeter
CMC: carboxymethylcellulose
CP: conditional power
CRF: case report form
CRO: Contract Research Organization
CRP: C-reactive protein
DBP: diastolic blood pressure
dL: deciliter
ECG: electrocardiogram
EEA: European Economic Area
e.g.: exempli gratia
EN: European Norm
F: Fahrenheit
FDA: Food and Drug Administration
fl: fluid
FLOW: First Loss Of Weight
FTO: fat mass and obesity associated
g: gram
GCP: Good Clinical Practices
GED: general educational development
GLOW: Gelesis Loss Of Weight
h: hour
HbA1c: glycosylated hemoglobin
HDL: high-density lipoprotein
HOMA-IR: homeostasis model assessment-insulin resistance
ICH: International Conference on Harmonisation
i.e.: id est
in: inch
ISO: International Organization for Standardization
ITT: intention-to-treat
IWQOL: impact of weight on quality of life
kcal: kilocalorie

KCNJ11: potassium voltage-gated channel subfamily J member 11
kg: kilogram
L: liter
lb: pound
LDL: low-density lipoprotein
LEPR: leptin receptor
MA: Massachusetts
MC4R: melanocortin-4 receptor
M.D.: Medical Doctor
mg: milligram
M.I.: middle initial
min: minute
mL: milliliter
mm Hg: millimeters of mercury
mmol: millimole
mol: mole
µU: microunit
n: number
NEGR1: neuronal growth regulator 1
NPC1: Niemann-Pick disease, type C1
oz: ounce
PCSK1: proprotein convertase subtilisin/kexin type 1
pH: power of hydrogen
pm: post meridiem
PP: per protocol
PPARG: peroxisome proliferator-activated receptor gamma
QEWP-R: questionnaire on eating and weight patterns-revised
SADE: serious adverse device effect
SAE: serious adverse event
SAP: Statistical Analysis Plan
SAS: Statistical Analysis System
SBP: systolic blood pressure
SD: standard deviation
SH2B1: SH2B adapter protein 1
SLC16A13: solute carrier family 16 member 13
Srl.: società a responsabilità limitata
TCF7L2: transcription factor 7-like 2
TEAE: treatment-emergent adverse event
TSH: thyroid-stimulating hormone
UADE: unanticipated adverse device effect
USADE: unanticipated serious adverse device effect
US: United States
USA: United States of America
WHO: World Health Organization

5. INTRODUCTION AND RATIONALE

5.1 Disease Background

Overweight (body mass index (BMI) ≥ 25 and < 30) and obesity (BMI ≥ 30) are becoming major health problems worldwide (1). The overweight/obesity epidemic was first noted in US and then spread to other industrialized nations; it is now being seen even in developing countries (2). The World Health Organization (WHO) estimated that the worldwide prevalence of obesity has nearly doubled between 1980 and 2008. In 2008, approximately 500 million adults around the globe were obese and in 2014, this number reached 600 million.

Overweight and obesity are responsible for increased morbidity and mortality (3). The comorbid conditions associated with overweight/obesity include cancer, coronary heart disease, delayed puberty, depression, disability, dyslipidemia, gallbladder disease, gout, hypertension, liver disease, osteoarthritis, respiratory dysfunction, sleep apnea, sexual impairment, social discrimination, type 2 diabetes, and other practical limitations and challenges. Weight loss of at least 5 to 10% appears to lower the risk of many of these comorbidities (4).

Overweight and obesity are chronic conditions and this characteristic should be considered when facing overweight and obese individuals. Management of overweight and obesity includes hypocaloric diet, exercise, behavior modification, device (e.g., intragastric balloon), drug, and surgery (bariatric surgery) (1, 5, 6, 7). The therapeutic benefit of all currently available anti-obesity tools is limited by their marginal efficacy, variable tolerability and safety profiles, and poor compliance.

The intragastric balloon is an intervention designed to reduce stomach volume (7), but there are conflicting data on sustained weight loss and no clear data indicating a decrease in mortality. Side effects include balloon movement, nausea, vomiting, pain, and stomach ulceration.

The results from bariatric surgery suggest that limiting the functional volume of the stomach is an effective modality for the treatment of obesity (6). However, because of the risk of peri-operative complications and the relatively high cost, bariatric surgery is usually reserved for the severely obese subjects.

A need exists for a product that is easy to use, safe, and effective at inducing weight loss. Interventions which act mechanically by occupying stomach volume, increasing the elastic modulus and viscosity of the upper gastrointestinal content, and extending gastric emptying time, could potentially be very beneficial.

A medical device which induces satiety and decreases hunger could result in decreased caloric intake and weight loss. The advantage of such a medical device is that it would

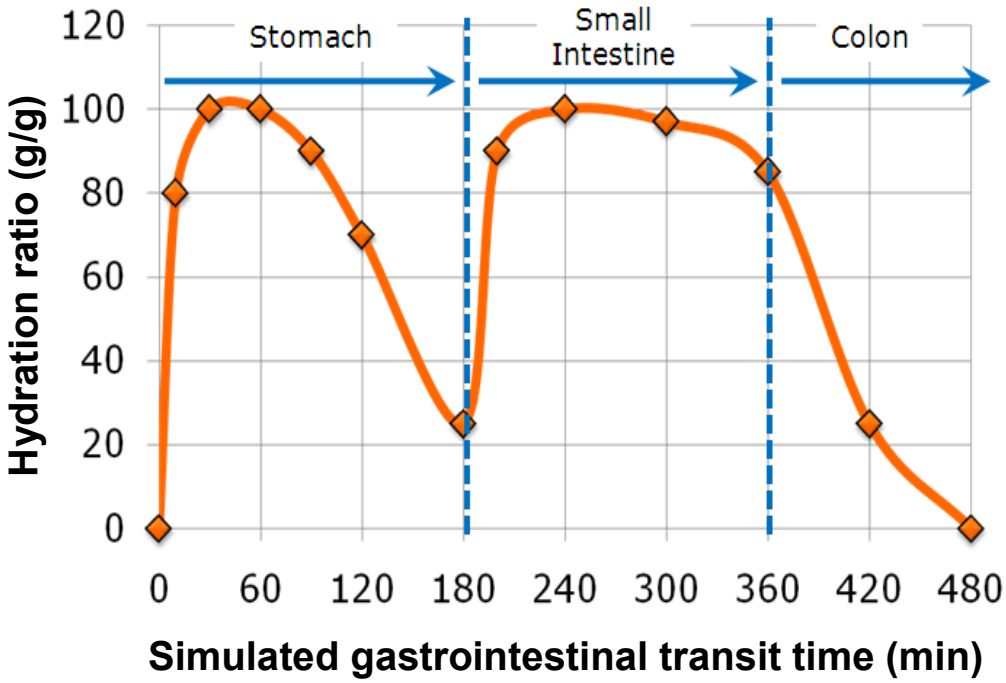
not require to drastically restrict food choices and would circumvent the challenge of unacceptable hunger levels which has derailed so many dietary interventions in the past.

5.2 Investigational Product

Gelesis100 is a novel, biocompatible hydrogel, composed of carboxymethylcellulose (CMC) sodium salt (E466) cross-linked with citric acid (E330). More than 99% of Gelesis100 consists of CMC and the rest is composed of citric acid. CMC and citric acid are safe food additives for use within the European Union (*European Directive 95/2/EC on Food Additives other than Colors and Sweeteners*) and are listed in the *List of Dietary Supplement Ingredients in use before October 15, 1994* published by the National Nutritional Food Association. In the proposed study, Gelesis100 will be used as a medical device. It is considered as a Class III device in Europe, a Class IV device in Canada, and a non-significant risk device in US.

Following ingestion of the Gelesis100 (capsule presentation), the capsule disintegrates in the stomach and releases a hydrogel which is capable of absorbing water solutions up to 100 times its original weight in the gastrointestinal environment. The Gelesis100 device hydrates in the stomach and converts a volume of liquids into a volume of small, distinct gel particles. The hydrated gel particles mix homogenously with ingested foods, creating a larger volume with a higher elasticity and viscosity of the stomach and small intestine contents. For example, 2.25 g of Gelesis100 will create a volume of approximately 225 mL. The created volume does not exceed the volume of liquid present, minimizing the risk of distension. The hydration rate of Gelesis100 in the different parts of the gastrointestinal tract has been demonstrated *in vitro* (Figure 1). Variations in its hydration capacity are mainly related to variations of the pH and ionic strength of the external solutions. The transit time reported in Figure 1 is only an example. Transit time is affected by the meal size and content.

Figure 1. Performance of Gelesis100 in simulated gastrointestinal conditions.



By occupying the gastric and intestinal cavities and by increasing the elasticity and the viscosity of the ingested foods, Gelesis100 induces satiety and reduces food intake, thereby contributing to weight reduction. Gelesis100 partially degrades in the large intestine and loses its three dimensional matrix structure and most of its absorption capacity. The water is absorbed from the hydrogel back in the colon and the device is expelled in the feces.

All relevant information concerning Gelesis100 is available in the Investigator's Brochure (8). This Clinical Investigation Plan will summarize the available clinical data.

5.2.1 Clinical Data

5.2.1.1 Effect on Satiety and Hunger

This study was aimed to assess the effects of a single administration of Gelesis100 on satiety and hunger (9). The study was conducted at the Agostino Gemelli Hospital, Rome, Italy. Ninety-five subjects were studied (Table 1). Study subjects received 2 g of Gelesis100 versus placebo before breakfast, lunch, and dinner, in a double-blind, cross-over fashion. There was a 2-day washout period between each administration of Gelesis100 for each subject. Meals consisted of habitual intake and were consumed at home. Satiety was assessed using a self-administered questionnaire immediately, and 30 and 60 min after meal. The questionnaire included 5 options to score the feeling of satiety: not at all (score 0), a little (score 1), enough (score 2), very (score 3), and very much (score 4). Hunger was assessed using the same type of questionnaire before meal.

Table 1. Clinical characteristics of the 95 study subjects.

Gender (n)		Age (years)		BMI*	
Male	Female	Mean ± SD	Range	Mean ± SD	Range
22	73	41 ± 12	19-67	31.1 ± 7.5	18.0-55.9

*Twenty-one subjects had normal (or subnormal) BMI, 22 were overweight, and 52 were obese.

Gelesis100 significantly increased the feeling of satiety at 30 min after breakfast and dinner (Table 2) and at 60 min after lunch and dinner (Table 3).

Table 2. Satiety scores (mean ± SD) at 30 min post-meal.

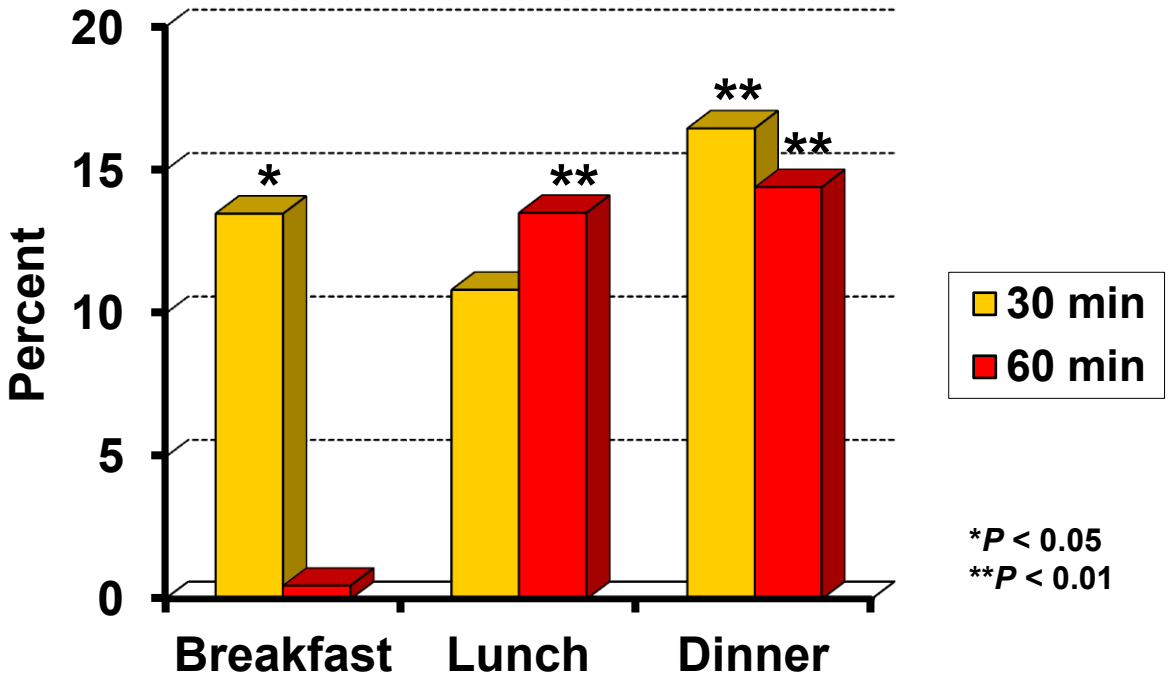
Meal	Gelesis100	Placebo	*P* value
Breakfast	1.85 ± 0.93	1.63 ± 0.95	0.037
Lunch	1.84 ± 1.14	1.66 ± 0.87	0.071
Dinner	1.98 ± 0.97	1.70 ± 1.01	0.004

Table 3. Satiety scores (mean ± SD) at 60 min post-meal.

Meal	Gelesis100	Placebo	*P* value
Breakfast	2.13 ± 1.00	2.12 ± 0.83	0.960
Lunch	2.35 ± 1.06	2.07 ± 0.86	0.007
Dinner	2.46 ± 1.12	2.15 ± 0.99	0.006

The placebo-adjusted effect of Gelesis100 on satiety (first meal effect) is reported in Figure 2.

Figure 2. Placebo-adjusted change in post-meal satiety scores (%) after Gelesis100 administration.



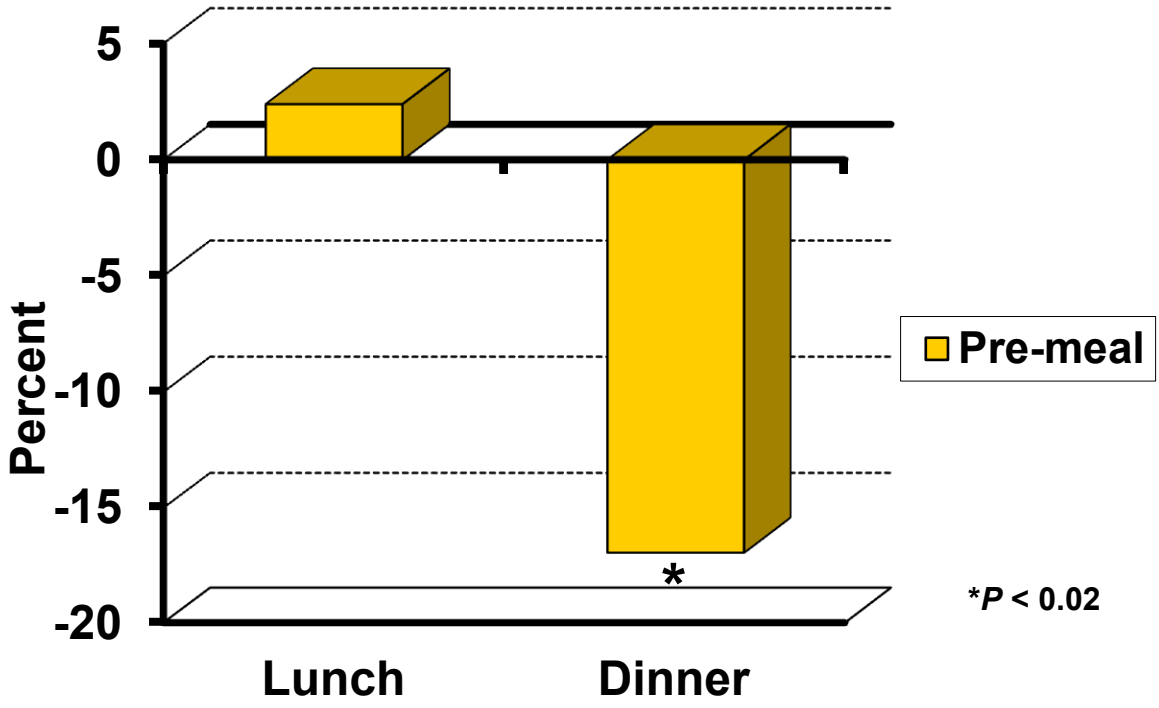
The administration of Gelesis100 before lunch significantly decreased the feeling of hunger before the subsequent dinner (Table 4).

Table 4. Hunger scores (mean ± SD) before lunch and dinner following Gelesis100/Placebo administration before breakfast and lunch, respectively.

Time	Gelesis100	Placebo	*P* value
Before lunch	1.71 ± 1.00	1.67 ± 0.83	0.702
Before dinner	1.47 ± 1.16	1.77 ± 0.98	0.011

The placebo-adjusted effect of Gelesis100 on hunger (second meal effect) is reported in Figure 3.

Figure 3. Placebo-adjusted change in pre-meal hunger scores (%) before lunch and dinner, after Gelesis100 administration before breakfast and lunch, respectively.



Treatment with Gelesis100 was safe and well tolerated. Fifteen subjects (15.8%) reported at least 1 symptom during the study. No detailed information was recorded as to whether the symptoms occurred after the administration of Gelesis100 or placebo (or both). Gastrointestinal symptoms (solicited adverse events "AEs") were reported in 13 subjects (13.7%) during the study (Table 5).

Table 5. Gastrointestinal symptoms during Gelesis100/Placebo administration in 95 subjects.

Symptoms*	Number of subjects	Percentage of subjects
Nausea	7	7.4
Constipation	4	4.2
Stomach ache	4	4.2
Vomiting	1	1.1
Diarrhea	1	1.1

*No information was recorded as to whether the symptoms occurred after the administration of Gelesis100 or placebo.

Three subjects (3.2%) reported more than 1 gastrointestinal symptom during the study: 2 reported 2 symptoms (stomach ache and diarrhea, nausea and constipation) and 1 reported 3 symptoms (nausea, vomiting, and stomach ache). Of the 7 subjects who

reported nausea during the study, all had a medical history of at least 1 gastrointestinal disorder (esophagitis, epigastralgia, colitis, constipation, and proctitis). Non-gastrointestinal symptoms (isolated headaches) were reported in 2 subjects (2.1%) during the study. No serious AE (SAE) was observed during the study.

In conclusion, a single administration of Gelesis100 significantly increases the post-meal feeling of satiety in humans. The administration of Gelesis100 before lunch significantly decreases the feeling of hunger before the subsequent dinner. The treatment is safe and well tolerated.

5.2.1.2 Effect on Body Weight

This study (FLOW = First Loss Of Weight) was aimed to assess the effect of repeated administration of Gelesis100 on body weight (10). The study was conducted at 5 sites in 3 European countries (Denmark, Czech Republic, and Italy). One hundred twenty-eight subjects were randomized into 3 arms: Gelesis100 2.25 g, Gelesis100 3.75 g, or placebo. Subjects received 5 capsules of Gelesis100 or placebo before lunch and dinner, in a double-blind and parallel-group fashion. A hypocaloric diet (-600 kcal/day) was prescribed to all subjects. The duration of the treatment was 12 weeks. One hundred twenty five subjects had at least one post-baseline assessment of body weight (intention-to-treat "ITT" population). Forty-two of the ITT subjects were on Gelesis100 2.25 g, 41 on Gelesis100 3.75 g, and 42 on placebo (Table 6). One hundred ten subjects completed the key visit of the study at Day 87 for the assessment of body weight. One hundred twenty-six subjects provided safety data. The primary efficacy endpoint was assessed by analysis of covariance (ANCOVA) model in the ITT population with baseline weight, gender, and BMI status as covariates.

Table 6. General characteristics of the ITT population at baseline.

Parameter	Gelesis100 2.25 g (n = 42)	Gelesis100 3.75 g (n = 41)	Placebo (n = 42)
Male (n)	13 (31%)	14 (34%)	13 (31%)
Female (n)	29 (69%)	27 (66%)	29 (69%)
Age (years)*	42.4 ± 12.3	46.1 ± 11.2	44.0 ± 11.7
BMI*	31.2 ± 2.3	31.8 ± 2.5	32.0 ± 2.3
Overweight (n)	14 (33%)	12 (29%)	12 (29%)
Obese (n)	28 (67%)	29 (71%)	30 (71%)
Glucose (mg/dL)* Glucose (mmol/L)*	93 ± 10 5.18 ± 0.54	94 ± 9 5.20 ± 0.50	96 ± 10 5.31 ± 0.58

*Mean ± SD.

Body weight decreased significantly at Day 87 in subjects on Gelesis100 2.25 g with a placebo-adjusted weight loss of 2.0% and a total body weight loss of 6.1% (Table 7).

Table 7. Body weight (% change from baseline) at Day 87 in the ITT population.

Arm	Number of subjects	Mean ± SD	*P* value (versus placebo)
Gelesis100 2.25 g	42	-6.1 ± 5.1	0.026
Gelesis100 3.75 g	41	-4.5 ± 4.5	0.859
Placebo	42	-4.1 ± 4.4	-

Subjects on Gelesis100 2.25 g had higher rate of weight loss ≥ 10% and lower rate of weight gain (Table 8). Lower tolerability and compliance may explain the observed efficacy result with Gelesis100 3.75 g.

Table 8. Body weight response at Day 87 in the ITT population.

Parameter	Gelesis100 2.25 g (n = 42)	Gelesis100 3.75 g (n = 41)	Placebo (n = 42)
Weight gain	3 (7%)	9 (22%)	7 (17%)
Weight loss < 5%	21 (50%)	13 (32%)	18 (43%)
Weight loss ≥ 5%	18 (43%)	19 (46%)	17 (40%)
Weight loss ≥ 10%	11 (26%)	5 (12%)	5 (12%)

The extent of weight loss at Day 87 was more pronounced in subjects on Gelesis100 2.25 g with impaired fasting glucose at baseline. The placebo-adjusted weight loss was 5.3% and the total body weight loss was 10.9% (Table 9). There was a significant negative correlation between fasting glucose at baseline and change in body weight at Day 87 in subjects on Gelesis100 2.25 g (r = -0.50; $P < 0.001$) contrasting with a lack of significant correlation in Gelesis100 3.75 g arm (r = -0.01; $P = 0.968$) and placebo arm (r = -0.06; $P = 0.708$).

Table 9. Body weight (% change from baseline) at Day 87 in the ITT population in subjects with impaired fasting glucose at baseline.

Arm	Number of subjects	Mean ± SD	*P* value (versus placebo)
Gelesis100 2.25 g	9	-10.9 ± 4.3	0.019
Gelesis100 3.75 g	9	-4.2 ± 5.7	0.348
Placebo	11	-5.6 ± 4.8	-

Treatment with Gelesis100 was safe and well tolerated. Thirty-one subjects (74%) on Gelesis100 2.25 g, 35 subjects (85%) on Gelesis100 3.75 g, and 36 subjects (84%) on placebo reported at least 1 AE during the study (mainly gastrointestinal AEs). Bloating, flatulence, abdominal pain, and diarrhea were the most common gastrointestinal AEs with lower prevalence in Gelesis100 2.25 g compared to placebo and Gelesis100 3.75 g

arms (Table 10). Common cold and headache were the most common non-gastrointestinal AEs. SAEs were observed in 3 subjects on placebo (gallstone and abdominal pain). The AEs were usually of mild intensity, occurred at different times during the course of the study, and resolved within 1 week in most cases.

Table 10. Gastrointestinal AEs* in the safety population.

Parameter	Gelesis100 2.25 g (n = 42)	Gelesis100 3.75 g (n = 41)	Placebo (n = 43)
Any gastrointestinal AE	25 (60%)	31 (76%)	32 (74%)
Bloating**	12 (29%)	15 (37%)	16 (37%)
Flatulence**	11 (26%)	15 (37%)	13 (30%)
Abdominal pain**	9 (21%)	12 (29%)	15 (35%)
Diarrhea**	8 (19%)	10 (24%)	16 (37%)

*Gastrointestinal AEs were solicited and recorded through a questionnaire. **Similar AEs are grouped under one main term.

Dropout after randomization occurred in 2 subjects (5%) on Gelesis100 2.25 g, 10 subjects (24%) on Gelesis100 3.75 g, and 9 subjects (21%) on placebo. No AE was responsible for the dropout with Gelesis100 2.25 g.

In conclusion, repeated administration of Gelesis100 (2.25 g twice daily) over 12 weeks significantly decreases the body weight in overweight and obese subjects, especially in subjects with impaired fasting glucose at baseline. The treatment is safe and well tolerated.

5.3 Rationale

Gelesis100 increases the volume and elasticity of the stomach and small intestine contents, and thus, inducing satiety and reducing food intake. Through its mechanical and non-pharmacological approach, Gelesis100, as a medical device, is a product that is well-positioned to overcome the limitations of the current weight-loss tools and fulfill the overwhelming unmet medical need for a safe and effective weight-loss product in overweight and obese subjects, especially in those with impaired fasting glucose.

6. OBJECTIVES

This study has the following objectives:

6.1 Primary

- To assess the decrease in body weight after repeated administration of Gelesis100 over a period of 168 days in overweight and obese subjects with and without type 2 diabetes ("placebo-adjusted" or "difference with placebo" weight loss ≥ 3.0%)
- To assess the body weight loss of at least 5% after repeated administration of Gelesis100 over a period of 168 days in overweight and obese subjects with and without type 2 diabetes (≥ 35% of subjects on Gelesis100)

6.2 Secondary

- To assess the decrease in serum insulin after repeated administration of Gelesis100 over a period of 168 days in overweight and obese subjects with and without type 2 diabetes
- To assess the decrease in insulin resistance (homeostasis model assessment-insulin resistance "HOMA-IR") after repeated administration of Gelesis100 over a period of 168 days in overweight and obese subjects with and without type 2 diabetes
- To assess the decrease in plasma glucose after repeated administration of Gelesis100 over a period of 168 days in overweight and obese subjects with and without type 2 diabetes
- To assess the decrease in glycosylated hemoglobin (HbA1c) after repeated administration of Gelesis100 over a period of 168 days in overweight and obese subjects with and without type 2 diabetes
- To demonstrate safety and tolerability similar to placebo or clinically acceptable of repeated administration of Gelesis100 over a period of 168 days in overweight and obese subjects with and without type 2 diabetes

7. DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-amount study using 1 amount of Gelesis100.

At the end of this study, an extension study will be proposed to all subjects who have completed 24 weeks of treatment and lost at least 3% of their body weight from baseline in order to assess the effectiveness and safety of Gelesis100 after an additional exposure of 24 weeks on an open-label basis.

8. POPULATION

The population will include overweight and obese subjects with and without type 2 diabetes.

8.1 Number of Subjects

Approximately 460 subjects will be randomized in this study (approximately 230 on active product and 230 on placebo). The selection and enrollment of subjects through advertisement is highly recommended. Subjects who once failed to meet the inclusion/exclusion criteria will not be re-screened (except for fasting plasma glucose and serum lipids, upon approval from the Sponsor).

8.2 Countries and Sites

The study will be conducted in US, Canada, and several European countries in approximately 38 sites.

The lists of Advisors, Investigators, investigation sites, laboratories, and other parties are reported in separate documents. The Sponsor will update and maintain these lists and communicate them with the Clinical Study Report.

8.3 Inclusion Criteria

1. Male and female ambulatory subjects (it is recommended to have at least 45% of each gender)
2. Age ≥ 22 years and ≤ 65 years
3. BMI ≥ 27 and ≤ 40 (it is recommended to have at least 70% of subjects with BMI < 35 and body weight < 120 kg in at least 92% of all subjects; subjects with BMI < 30 should have at least one comorbidity including untreated or metformin-treated type 2 diabetes, untreated dyslipidemia with low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL (≥ 3.37 mmol/L) and/or triglycerides ≥ 150 mg/dL (≥ 1.69 mmol/L) or drug-treated dyslipidemia, and untreated hypertension with supine systolic blood pressure (SBP) ≥ 140 mm Hg and/or supine diastolic blood pressure (DBP) ≥ 90 mm Hg based on the mean of two consecutive readings or drug-treated hypertension)
4. Fasting plasma glucose ≥ 90 mg/dL and ≤ 145 mg/dL (≥ 5.0 mmol/L and ≤ 8.1 mmol/L); it is recommended to have approximately 45 to 55% non-diabetic normoglycemic subjects (fasting glucose ≥ 90 mg/dL and < 100 mg/dL or ≥ 5.0 mmol/L and < 5.6 mmol/L) and the rest, non-diabetic impaired fasting glucose subjects (fasting glucose ≥ 100 mg/dL and < 126 mg/dL or ≥ 5.6 mmol/L and < 7.0 mmol/L) or diabetic subjects either:
   - untreated (fasting glucose ≥ 126 mg/dL and ≤ 145 mg/dL or ≥ 7.0 mmol/L and ≤ 8.1 mmol/L)
   - or metformin-treated (metformin dose ≤ 1500 mg/day, fasting glucose ≤ 145 mg/dL or ≤ 8.1 mmol/L)
5. Ability to follow verbal and written instructions
6. Informed Consent Form signed by the subjects

8.4 Exclusion Criteria

1. Pregnancy (or positive serum or urine pregnancy test(s) in females of childbearing potential) or lactation
2. Absence of medically approved contraceptive methods in females of childbearing potential (e.g., hysterectomy, non-oral contraceptive medications or intrauterine device combined with a barrier method, two combined barrier methods such as diaphragm and condom or spermicide, or condom and spermicide; bilateral tubal ligation and vasectomy are not acceptable contraceptive methods)
3. History of allergic reaction to CMC, citric acid, sodium stearyl fumarate, raw cane sugar, gelatin, and titanium dioxide
4. Administration of investigational products within 1 month prior to Screening Visit
5. Subjects who stopped smoking within 6 months prior to Screening Visit or considering smoking cessation during the study
6. Subjects anticipating surgical intervention during the study
7. Known type 1 diabetes
8. History of eating disorders including binge eating (except mild binge eater)
9. Weight change > 3 kg within 3 months prior to and during the Screening period
10. Supine SBP > 160 mm Hg and/or supine DBP > 95 mm Hg (mean of two consecutive readings)
11. Angina, coronary bypass, or myocardial infarction within 6 months prior to Screening Visit
12. History of swallowing disorders
13. Esophageal anatomic abnormalities (e.g., webs, diverticuli, rings)
14. History of gastroesophageal reflux disease
15. History of gastric or duodenal ulcer
16. History of gastroparesis (chronic nausea, vomiting, heartburn, …)
17. History of gastric bypass or any other gastric surgery
18. History of small bowel resection (except if related to appendectomy)
19. History of intestinal stricture (e.g., Crohn's disease)
20. History of intestinal obstruction or subjects at high risk of intestinal obstruction including suspected small bowel adhesions
21. History of abdominal radiation treatment
22. History of pancreatitis
23. History of malabsorption
24. History of sucrose intolerance
25. Laxative users
26. History of hepatitis B or C
27. History of human immunodeficiency virus
28. History of cancer within the past 5 years (except adequately-treated localized basal cell skin cancer or *in situ* uterine cervical cancer)
29. Any other clinically significant disease interfering with the assessments of Gelesis100, according to the Investigator (e.g., disease requiring corrective treatment, potentially leading to study discontinuation)
30. Abnormal serum thyroid-stimulating hormone (TSH)
31. HbA1c > 8.5% (> 69 mmol/mol)

32. Serum low-density lipoprotein cholesterol ≥ 190 mg/dL (≥ 4.93 mmol/L)
33. Serum triglycerides ≥ 500 mg/dL (≥ 5.65 mmol/L)
34. Positive test for drugs in the urine
35. Any relevant biochemical abnormality interfering with the assessments of Gelesis100, according to the Investigator
36. Anti-obesity medications (including herbal preparations) within 1 month prior to Screening Visit
37. Antidiabetic medications within 1 month prior to Screening Visit (except stable dose of metformin, ≤ 1500 mg/day, for at least 1 month in subjects with type 2 diabetes)
38. Systemic corticosteroids within 1 month prior to Screening Visit
39. Thyroid hormones or preparations within 1 month prior to Screening Visit (except stable dose of replacement therapy for at least 1 month)
40. TSH suppression therapy for thyroid cancer
41. Estrogen within 1 month prior to Screening Visit (except stable dose of replacement therapy for at least 1 month or non-oral contraceptive for at least 3 months)
42. Any other medication or product known to cause weight loss or weight gain within 1 month prior to Screening Visit
43. Change in medications treating dyslipidemia within 1 month prior to Screening Visit (including change in dose)
44. Change in medications treating hypertension within 1 month prior to Screening Visit (including change in dose)
45. Medications requiring mandatory administration with meal at lunch or dinner
46. Anticipated requirement for use of prohibited concomitant medications (see Section 9.2.1)

9. TREATMENT

9.1 Investigational Product

Gelesis100 (medical device in capsule) and matching placebo will be used. Each capsule of Gelesis100 contains approximately 750 mg of CMC sodium salt cross-linked with citric acid, and 11 mg of sodium stearyl fumarate. Each capsule of placebo contains approximately 900 mg of raw cane sugar (sucrose).

The envelopes of Gelesis100 and placebo capsules are provided by Capsugel. They each contain 126 mg of gelatin and 4 mg of titanium dioxide. The gelatin component is an animal-derived product. According to Capsugel, the gelatin undergoes stringent preliminary physical, chemical, and microbiological tests before it is released into production by the Capsugel quality control department.

9.1.1 Selection of Gelesis100 Amount

Since Gelesis100 hydrates approximately 100 times its weight in the gastrointestinal tract, the proposed amount of 2.25 g of Gelesis100 (3 capsules before lunch and dinner) will expose the subjects to a volume of approximately 225 mL. This is well below the estimated volume of the human stomach which is about 900 mL (11) but is similar to the amount used in the FLOW study showing significant decrease in body weight and a good safety profile.

9.1.2 Selection of Placebo

To minimize the risk of unblinding in case the capsules are opened accidentally or intentionally, raw cane sugar was selected as placebo since it has the same color and shape as Gelesis100. Raw cane sugar contains sucrose (simple carbohydrate). The daily amount of sucrose (< 6 g/day) administered through placebo capsules is clinically acceptable (12) and has no significant health impact (including in diabetic subjects), especially if the subjects are following the dietary recommendations of the study. Indeed, substantial evidence from clinical studies demonstrates that dietary sucrose does not increase glycemia more than isocaloric amounts of starch (13).

9.1.3 Packaging and Labeling

The study product will be packaged in polypropylene bottles (3 capsules per bottle) and the bottles will be packaged in weekly boxes. Each weekly box will contain allowance for 1 additional day of dosing (i.e., 2 x 3 additional capsules) in the event the subsequent visit is delayed or the study product is damaged or lost. Each bottle will be appropriately labeled in accordance with the regulatory specifications and requirements. Each product (Gelesis100 or placebo) will have a unique serial number as part of the label. The labels will have 6 languages: English, French, Danish, Czech, Italian, and Spanish, in accordance with language requirements in US, Canada, and the European Economic Area (EEA) [status: 1/2007].

9.1.4 Responsibilities

The Investigator (or designee) will maintain an accurate record of receipt of the investigational product as shipped by the Sponsor, including the date received, the batch number, and the serial number. One signed copy of this receipt will be returned to the Sponsor when the contents of the shipment have been verified.

The personnel in charge of the storage and dispensation of the investigational product will insure that the product is securely maintained as specified by the Sponsor and in accordance with the regulatory requirements.

The investigational product will be used for the purpose of this study only, and will be dispensed in accordance with the Investigator's prescription. It is the responsibility of the Investigator to ensure that an accurate record of investigational product dispensed and

returned is maintained. The product disposition record will specify the amount dispensed to each subject and the date of dispensation. The inventory record will be available for inspection at any time. At the completion of the study, the Investigator (or designee) will make available copies of this inventory record to the Sponsor (or designee) upon request.

Any quality issue noticed with the receipt or use of the investigational product by the Investigator (or designee) should be promptly notified to the Sponsor (or designee).

9.1.5 Storage Conditions

The investigational product will be sent by the Sponsor to the Investigator according to local regulatory requirements. It will be stored at the site, in a secure and safe place, between 5°C (41°F) and 30°C (86°F), under the responsibility of the Investigator or other authorized individual.

9.1.6 Administration Method

At each dosing of study product, a subject will consume 3 capsules. Damaged capsules should not be used. Capsules will be self-administered orally by the subjects 20 to 30 min before meals at lunch and dinner, with approximately 100 mL of water. After the capsules are taken, subjects will wait 5 to 10 min and then proceed to slowly drink 500 mL of water over a period of up to 10 min. After this water intake, subjects will wait an additional 10 min before beginning to consume their meal in a slow manner. Drinking additional water during and after the meal is highly recommended.

9.1.7 Treatment of Overdose

Overdose with Gelesis100 may cause nausea, vomiting, flatulence, bloating, abdominal pain, constipation, diarrhea, or other unexpected side effects. The Investigator is responsible for any decision regarding the treatment of the overdose.

9.1.8 Compliance Assessment

Compliance will be assessed by counting of capsules remaining in each bottle, at each visit.

Product accountability will be under Investigator's direct supervision. The appropriate electronic case report form (CRF) will be completed regarding the dosing and the treatment assignment.

9.1.9 Retrieval and/or Destruction

At the completion of the study, investigational product, including all empty, partially used, and unused bottles, will be returned to the Sponsor (or designee). Detailed

treatment and accountability logs will be established and countersigned by the Investigator and the Monitoring Team Representative (or designee).

The Investigator will not destroy the unused investigational product unless requested officially in writing by the Sponsor.

9.2 Concomitant Medication

9.2.1 Prohibited Medication

- Oral contraceptives
- Anti-obesity medications or other medications (including herbal preparations especially those containing amphetamine-like compounds) for weight reduction
- Antidiabetic medications (except stable dose of metformin, ≤ 1500 mg/day, in subjects with type 2 diabetes already on treatment)
- Systemic corticosteroids (oral, rectal, injectable)
- Thyroid hormones or preparations (except stable dose of replacement therapy in subjects already on thyroid hormones or preparations)
- Diuretics
- Estrogen (except stable dose of replacement therapy or non-oral contraceptive in subjects already on treatment)
- Any other medication or product known to cause weight loss or weight gain
- Change in medications treating dyslipidemia (including change in dose)
- Change in medications treating hypertension (including change in dose)
- Any medication affecting gastrointestinal motility
- Addictive medications including amphetamines, barbiturates, cannabinoids, cocaine, opiates, and phencyclidine

The intake of prohibited medication for more than 7 days in case of oral formulation and at least once in case of injectable formulation is a major protocol deviation and will result in subject discontinuation from the study. The oral intake of prohibited medication for 7 days or less is a minor protocol deviation and will not result in subject discontinuation from the study.

9.2.2 Permitted Medication

- Non-oral medications used for contraception
- All other drugs than those listed in Section 9.2.1, if considered necessary for the subject, with a stable dose (when possible), at the discretion of the Investigator (if they are not taken within 2 h before and after the study product administration in case of oral drugs)

Subjects should avoid the intake of any oral drugs and/or vitamin supplements within 2 h before and after the study product administration to prevent a potential reduction in the

efficacy of these drugs/vitamin supplements (secondary to a decrease in their intestinal absorption).

At selected sites where vitamins are measured, subjects taking vitamin supplements should continue their intake without any change of the dose or the timing of administration during the study.

9.3. Diet and Life-Style Recommendations

9.3.1 Diet

During the entire study (from the Baseline Visit to the last Follow-up Visit), a hypocaloric diet will be prescribed to all subjects. The energy requirement will be calculated by the dietitian based on the estimated basal metabolism rate and the physical activity of each subject at the Screening Visit using the Harris-Benedict equation (14). From this amount of energy, 300 kcal/day will be subtracted to obtain the recommended hypocaloric diet. The energy content will not be less than 1,200 kcal/day.

The daily dietary intake will include approximately 45% to 50% of calories from carbohydrate, up to 30% of calories from fat (< 10% saturated fat, < 200 mg cholesterol), and 20% to 25% of calories from protein. Meals should be consumed slowly with water as instructed. The meal time should remain relatively unchanged during the study. The interval between lunch and dinner should be at least 5 h. The average daily alcohol consumption should be ≤ 20 g/day (or ≤ 140 g/week). The daily sodium intake of each subject should remain unchanged.

The compliance of the subjects with the proposed diet will be assessed by a dietitian at each dietary interview during the study. The instructions on water intake should be reinforced if there is an increase in serum albumin from baseline of more than 1 g/L at Visit 4 (Day 15), Visit 5 (Day 29), and Visit 9 (Day 85).

9.3.2 Life-Style

Subjects will be instructed to have moderate-intensity physical activity (e.g., 30 min walking every day) during the study.

Subjects will be instructed to continue, without change, their smoking habits during the study.

The compliance of the subjects with the proposed life-style will be assessed by the Investigator's Team at each visit during the study.

10. STUDY DURATION

10.1 Study Duration per Subject

10.1.1 Screening Period

The maximum duration of the screening period is 21 days.

10.1.2 Baseline Period

The duration of the baseline period is 1 day.

10.1.3 Treatment Period

The duration of the double-blind treatment period (active product versus placebo) is 168 days with a visit window of 2 or 3 days (see Section 12.1).

10.1.4 Post-Treatment Follow-up Period

The duration of the follow-up period is 28 days with a visit window of 3 days for Visit 14 but no visit window for Visit 13 (see Section 12.1).

10.2. Total Study Duration

The total study duration will be approximately 2 years (including approximately 1 and half years for enrollment). The start date is expected to be during the second half of 2014 and the end date during the first half of 2017.

11. STUDY ENDPOINTS

When hydrated, Gelesis100 has some weight by itself. At any time following the first day of Gelesis100 administration, subjects may accumulate up to 1 kg of hydrated Gelesis100 in their gastrointestinal tract. Therefore, it is likely to observe an initial weight gain during the first days or weeks of treatment until the extra weight is counter-balanced by the weight loss caused by Gelesis100. An interval of 2 days is required for any remaining Gelesis100 to be eliminated from the gastrointestinal tract. For these reasons, to ensure that the weight of Gelesis100 does not mask the true amount of weight loss, the end of treatment assessment of body weight and weight-related parameters will be performed on Day 171, approximately 60 h after the last administration of Gelesis100.

11.1 Effectiveness Endpoints

11.1.1 Co-Primary Endpoints

- Body weight (percent change from baseline to Day 171)
- Body weight responders (≥ 5% weight loss from baseline to Day 171)

11.1.2 Secondary Endpoints

- Plasma glucose status (normal, impaired, diabetic) (change from baseline to Day 171)
- Plasma glucose (percent change from baseline to Day 171)
- HOMA-IR (percent change from baseline to Day 171)
- HbA1c (change from baseline to Day 171)
- BMI (change from baseline to Day 171)

11.1.3 Tertiary Endpoints

- Body weight responders (≥ 10% weight loss from baseline to Day 171)
- Estimated excess body weight (percent change from baseline to Day 171)
- Body weight status (normal, overweight, obese) (change from baseline to Day 171)
- Waist circumference (change from baseline to Day 171)
- Serum insulin (percent change from baseline to Day 171)
- Serum C-reactive protein (CRP) (change from baseline to Day 171)
- Serum total cholesterol (percent change from baseline to Day 171)
- Serum LDL cholesterol (percent change from baseline to Day 171)
- Serum high-density lipoprotein (HDL) cholesterol (percent change from baseline to Day 171)
- Serum total cholesterol/HDL cholesterol ratio (change from baseline to Day 171)
- Serum triglycerides (percent change from baseline to Day 171)
- Supine and standing SBP and DBP (change from baseline to Day 171)
- Food intake (change from baseline to Day 169)
- Food habits (change from baseline to Day 169)
- Satisfaction (overall impression on Day 169)
- Impact of weight on quality of life (IWQOL) (change from baseline to Day 171) (at selected sites)

The secondary and tertiary effectiveness endpoints are for supportive purposes only.

11.2 Safety Endpoints

11.2.1 Adverse Events

- All AEs and SAEs (including ADEs and SADEs)

11.2.2 Physical Examination

- Full physical examination (excluding pelvic and rectal examination)

11.2.3 Vital Signs

- Supine and standing SBP and DBP
- Supine and standing heart rate

11.2.4 Laboratory Tests

- 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
- Vitamins including vitamin A, vitamins B_1, B_2, B_6, B_9, and B_{12}, vitamin D, and vitamin E (vitamins will be measured in approximately 60 subjects from the sites of Czech Republic and the site of Rome, Italy)

11.3 Assessment Methods

All the assessments, unless otherwise specified, will be performed in the morning (between approximately 7 am and 10 am), before product intake, on fasting subjects (10 to 12-h fast) with no moderate or intense physical activity within the past 12 h. Physical examination, dietary interview, and electrocardiogram (ECG) can be performed at any time during the day regardless of food or investigational product intake.

11.3.1 Clinical

11.3.1.1 Physical Examination

A full physical examination (excluding pelvic and rectal examination) will be performed by the Investigator. The physical examination will cover the following areas:
- general appearance
- eyes
- ears, nose, throat
- neck
- respiratory
- cardiovascular
- endocrine
- hepatic
- gastrointestinal
- genitourinary
- peripheral vascular
- neurological
- musculoskeletal
- extremities

- lymphatic
- dermatological
- allergies
- psychiatric

11.3.1.2 Body Weight

Body weight should be obtained with the subject wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study. The use of a balance-beam scale is recommended. If a digital scale is used, testing with standard weights is of particular importance. The scale needs to be calibrated within 12 months prior to the first Screening Visit and its precision should be verified every 4 months after the first Screening Visit. The floor surface on which the scale rests must be hard and should not be carpeted or covered with another soft material and the scale must not be moved during the entire duration of the study. The scale should be balanced with both weights at zero and the balance bar aligned. The subject should stand in the center of the platform as standing off-center may affect the measurement. The weights are moved until the beam balances (the arrows are aligned). The weight is read and recorded. Self-reported weights are not acceptable. Subjects must not read the scale themselves.

11.3.1.3 Waist Circumference

Waist circumference should be measured according to the established methods. It is taken at the midpoint between the lower rib margin and the iliac crest. The circumference should preferably be measured on subjects while they are semi-clothed (i.e., waist uncovered with the subjects wearing underclothes only). If it is not possible to follow this procedure, the alternative is to measure the circumference on subjects without heavy outer garments with all tight clothing, including the belt, loosened and with pockets emptied. Subjects should stand with their feet close together (no more than 15 cm apart) with their weight equally distributed on each leg. Subjects should be asked to breathe normally and at the time of the reading of the measurements asked to breathe out gently. This will prevent subjects from contracting their muscles or from holding their breath. A plastic metric tape should be used. The length of the tape should be checked before starting the study and the length should be re-checked against a standard measure at least once a month and the tape should be replaced as appropriate. The two sides of the tape should be differently colored or have a scale only on 1 side. If the tape is uniformly colored, with reading on both sides, 1 side should be blanked out. The tape should be held firmly and its horizontal position should be ensured. The tape should be loose enough to allow the recorder to place 1 finger between the tape and the subject's body. The importance of the tightness of the tape should be emphasized. It is recommended that the observer sits beside the subject while the readings are taken. Three measurements will be performed and recorded.

11.3.1.4 Blood Pressure

SBP and DBP will be measured using a calibrated device. The device will be a mercury sphygmomanometer with a cuff appropriate to the subject's arm girth (obesity cuff). If not available, another device may be used which is calibrated carefully in proportion to a

mercury sphygmomanometer. Aneroid manometer is not recommended. The calibration of the device will be according to the site-specific guidelines and requirements. The same model of device will be used for each subject throughout the study. Blood pressure should be measured under standardized conditions, on the same arm. Both SBP and DBP should be recorded. The disappearance of sound (Korotkov phase V) should be used for the diastolic reading. Blood pressure should be measured in both supine position (after the subject has rested comfortably for at least 5 min) and standing position (after 2 min). At the Screening Visit, supine blood pressure should be checked in both arms on two consecutive readings separated by 2 min. The arm with the higher SBP will be determined at this visit based on the mean of two consecutive readings, and blood pressure should be measured in this arm throughout the study. At each other visit, two readings of supine blood pressure separated by 2 min should be recorded.

11.3.1.5 Heart Rate

Heart rate (pulse) will be measured over 1 min at the time of the second measurement of supine blood pressure and at the time of the measurement of standing blood pressure and the results will be recorded.

11.3.1.6 Electrocardiogram

ECG will be obtained using a 12-lead cardiograph. The maintenance of the device will be according to the site-specific guidelines and requirements. ECG will be performed after a 15-min rest in supine position.

11.3.1.7 Binge Eating Disorder

The questionnaire on eating and weight patterns-revised (QEWP-R) abbreviated version will be used to identify subjects with binge eating (Appendix 1). Subjects are excluded from enrollment if the answer to question 11 is yes except if they are considered as mild binge eaters according to the Investigator's assessment.

11.3.1.8 Food Intake

Food intake will be assessed by food diary. The diary will include all the meals consumed during any 2 consecutive weekdays and 1 weekend day before the visit. The assessment will include global food intake (including fluid intake), carbohydrate intake, fat intake, protein intake, and fiber intake.

11.3.1.9 Food Habits

Food habits will be assessed by a questionnaire (Appendices 2 and 3).

11.3.1.10 Satisfaction

A questionnaire will record the thoughts of the subjects regarding the investigational product (Appendix 3). The questionnaire will be completed by the subjects at the last treatment visit.

11.3.1.11 Impact of Weight on Quality of Life

The IWQOL questionnaire will ask subjects at selected sites about the impact of weight on their quality of life (Appendix 4).

11.3.1.12 Adverse Events
All AEs and SAEs will be recorded (see Section 13).

11.3.2 Biological

11.3.2.1 Blood Parameters and Genomic Tests
Blood samples will be collected by venipuncture and shipped to the local or central laboratory as per laboratory instructions (provided in a laboratory manual).

Insulin resistance will be measured by HOMA-IR (15), which is calculated by multiplying fasting serum insulin (μU/mL) by fasting plasma glucose (mmol/L) and dividing by 22.5.

Serum amylase results will be reported as total serum amylase and pancreatic serum amylase.

Genomic tests will include the analysis of copy number variation of AMY1 gene (gene encoding salivary amylase) and additional analysis of several genes involved in obesity and type 2 diabetes (BDNF, CAPN10, FTO, KCNJ11, LEPR, MC4R, NEGR1, NPC1, PCSK1, PPARG, SH2B1, SLC16A13, and TCF7L2 genes). Blood samples for the extraction and analysis of deoxyribonucleic acid will be shipped to the central laboratory as per laboratory instructions. The results of genomic tests together with the results of serum amylase will be correlated to weight-related and metabolic parameters at baseline and their evolution during the study, in different populations.

The total blood requirement per subject for all blood samplings will be approximately 70 mL over approximately 31 weeks. An additional 25 mL of blood per subject will be drawn during the entire study at sites where vitamins should be measured and 5 mL of blood per subject will be drawn at a single visit for genomic tests.

11.3.2.2 Urine Parameters
Urine samples will be collected from a morning spot. The tests will be performed at the Investigator's site (pregnancy test, drug screen). The subjects should empty their bladder (and discharge the urine) around 6 am, drink approximately 1 glass of water, and wait approximately 2 h before the urine samplings.

Urine drug screen will detect amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, and phencyclidine.

12. VISITS

12.1 Schedule

This is an outpatient study (see Section 2 **Study Flow Chart**). The assessments of Visit 1 (Screening Visit) can be done over several days within the screening period. Visit 13

should occur 2 days after Visit 12. The other visits can take place within ± 2 days (up to Visit 9) and ± 3 days (after Visit 9) of the schedule.

Visit 13 should be avoided during the extended holiday period of December/January (the last week of December and the first 2 weeks of January). To reach this objective, Visit 2 should not be scheduled during the last 3 weeks of July.

12.2 Assessments

The following procedures will be performed (see Section 11 **Study Endpoints**):

12.2.1 Visit 1 (Screening Visit; Day -21 to -1)

- Informed consent (women of childbearing potential are requested to use a medically approved contraceptive method during the entire study)
- Demographic characteristics (gender, age, ethnic origin)
- Menopausal status (and estrogen replacement therapy status)
- Smoking status
- Medical history
- Physical examination
- Height
- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- ECG
- Binge eating disorder (QEWP-R)
- Dietary interview (calculation of the energy requirement)
- Serum pregnancy test (women of childbearing potential only)
- TSH
- Urine drug screen (test performed at the Investigator's site)
- HbA1c
- Hematology
- Blood chemistry
- Previous (within 1 month) and concomitant medication records
- AEs and SAEs records

12.2.2 Visit 2 (Baseline Visit; Day 0)

- Physical examination
- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary prescription)
- Food intake
- Food habits

- IWQOL
- Serum amylase (blood can be collected at any of the Visits 2, 3, 4, 5, 9, or 13)
- Genomic tests (blood can be collected at any of the Visits 2, 3, 4, 5, 9, or 13) (tests not mandatory)
- Serum pregnancy test (women of childbearing potential only)
- Urine pregnancy test (women of childbearing potential only) (test performed at the Investigator's site)
- Serum insulin
- HbA1c
- Serum CRP
- Hematology
- Blood chemistry
- Vitamins
- Concomitant medication record
- Randomization
- Dispensation of study product (administration begins the following day)
- AEs and SAEs records

12.2.3 Visit 3 (First Double-Blind Visit; Day 8 ± 2)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Plasma glucose
- Serum insulin
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records

12.2.4 Visit 4 (Second Double-Blind Visit; Day 15 ± 2)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Plasma glucose
- Serum insulin
- Serum albumin
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product

- AEs and SAEs records

12.2.5 Visit 5 (Third Double-Blind Visit; Day 29 ± 2)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Food intake
- Plasma glucose
- Serum insulin
- Serum albumin
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records

12.2.6 Visit 6 (Fourth Double-Blind Visit; Day 43 ± 2)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records

12.2.7 Visit 7 (Fifth Double-Blind Visit; Day 57 ± 2)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Food intake
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records

12.2.8 Visit 8 (Sixth Double-Blind Visit; Day 71 ± 2)

- Weight

- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records

12.2.9 Visit 9 (Seventh Double-Blind Visit; Day 85 ± 2)

- Physical examination
- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Food intake
- Serum pregnancy test (women of childbearing potential only)
- Serum insulin
- TSH (subjects on replacement therapy with thyroid hormones or preparations only)
- HbA1c
- Serum CRP
- Hematology
- Blood chemistry
- Vitamins
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records
- Reinforcement of study-related instructions

12.2.10 Visit 10 (Eighth Double-Blind Visit; Day 113 ± 3)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Food intake
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records

12.2.11 Visit 11 (Ninth Double-Blind Visit; Day 141 ± 3)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Food intake
- Concomitant medication record
- Investigational product accountability
- Dispensation of study product
- AEs and SAEs records

12.2.12 Visit 12 (Tenth Double-Blind Visit; Day 169 ± 3)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Food intake
- Food habits and satisfaction
- Concomitant medication record
- Investigational product accountability
- AEs and SAEs records

12.2.13 Visit 13 (First Follow-up Visit; Day 171; 2 days after Visit 12) (Last visit if entering extension study)

- New informed consent (subjects entering extension study)
- Physical examination
- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- IWQOL
- Serum pregnancy test (women of childbearing potential only)
- Serum insulin
- HbA1c
- Serum CRP
- Hematology
- Blood chemistry
- Vitamins
- Concomitant medication record
- AEs and SAEs records

12.2.14 Visit 14 (Second Follow-up Visit; Day 197 ± 3)

- Weight
- Waist circumference
- Vital signs (supine and standing blood pressure and heart rate)
- Dietary interview (dietary check)
- Concomitant medication record
- AEs and SAEs records

12.3 Definition of Source Data

The list of information considered as source data that must be shown in the subject's chart is provided in Appendix 5.

13. SAFETY MONITORING AND REPORTING

13.1 Adverse Event and Device Deficiency

13.1.1 Investigational Product in this Clinical Study

In this clinical study, the investigational product, Gelesis100, is considered as a medical device. Therefore, all safety monitoring and reporting procedures are governed by medical device guidelines and regulations.

13.1.2 Definitions

An AE is any untoward medical occurrence (sign, symptom, illness, abnormal laboratory value, or other medical event) in a subject, whether or not related to the investigational medical device. This includes events related to the procedures involved (any procedure in the Clinical Investigation Plan).

A SAE is any AE that:
- led to death
- resulted-in a life-threatening condition
- resulted-in a permanent impairment of a body structure or a body function
- required inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 h (elective hospitalizations and/or hospitalizations for treatment of pre-existing conditions that did not worsen from baseline are not considered AEs and should not be reported as SAEs)
- resulted-in a medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- led to fetal distress, fetal death or a congenital abnormality, or birth defect

A device deficiency is an inadequacy of the medical device with respect to its identity, quality, durability, and safety (e.g., use errors and inadequate labeling). Medical device

deficiency can lead to an adverse device effect (ADE) or a serious ADE (SADE) (see below).

For the purpose of this study and for reporting purposes, all device deficiencies that could have led to SAEs, if suitable action had not been taken or intervention had not been made, or if circumstances had been less fortunate, will also be considered as SAE.
An ADE is an AE with a reasonable causal relationship to the use of the investigational medical device (i.e., an AE assessed as either "most probably related" or "possibly related" to the use of medical device) (see Section 13.1.3).

An unanticipated ADE (UADE) is an ADE not previously reported or an ADE that occurs with specificity, severity, frequency, or outcome that is not consistent with the current Investigator's Brochure (8).

A SADE is a SAE with a reasonable causal relationship to the use of the investigational medical device (i.e., a SAE assessed as either "most probably related" or "possibly related" to the use of medical device). For Canada, this definition is equivalent to the Canadian definition of an incident.

An unanticipated SADE (USADE) is a SADE not previously reported or an SADE that occurs with specificity, severity, frequency, or outcome that is not consistent with the current Investigator's Brochure. In US, this definition is equivalent to the definition of an UADE in Medical Device Reporting regulation at Title 21.

13.1.3 Adverse Event and Device Deficiency Recording, Assessment, and Reporting Procedure

All AEs regardless of seriousness or relationship to the investigational medical device including those occurring during the screening period (after the signature of the Informed Consent Form) are to be recorded in the appropriate electronic CRF.

AEs reported by subject will be discussed in details and recorded by the Investigator at each visit. AEs will be collected until 28 days after the last administration of the investigational medical device (i.e., until subject terminates his/her participation in the study).

The Investigator should specify the date of onset, severity, action taken with respect to the investigational medical device, corrective treatment, outcome, and whether or not there is a reasonable possibility that the AE may have been caused by the use of the investigational medical device.

AEs are graded as follows:

- Mild: sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.

- Moderate: sign or symptom, which may be ameliorated by simple therapeutic measures, may interfere with usual activity.
- Severe: sign or symptom intense or debilitating and interfering with usual activities without being immediately life-threatening. Recovery is usually aided by therapeutic measures.
- Very severe: sign or symptom life-threatening. Urgent intervention indicated.

The assessment of the relationship of an AE to the use of the medical device is a clinical decision based on all available information at the time of the completion of the electronic CRF:

- Most probably related: follows a reasonable temporal sequence from medical device use, and cannot be reasonably explained by known characteristics of the subject's clinical data.
- Possibly related: follows a reasonable temporal sequence from medical device use, but could have been produced by the subject's clinical state regardless of the medical device.
- Probably not related: temporal association is such that the medical device use is not likely to have had any reasonable association with the observed event.
- Not related: no relationship to the use of the medical device is perceived.

Abnormalities of vital signs and laboratory results are to be recorded as AEs only if they are considered by the Investigator as clinically significant (symptomatic, requiring corrective treatment, leading to discontinuation, or fulfilling a seriousness criteria).

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the Screening Visit should be recorded as medical/surgical history.

In this study, the following events will be reported to the authorities on expedited basis:

- All SAEs (including SADEs) will be expeditiously reported to the relevant European Regulatory Authorities and the Ethics Committees.
- All newly discovered pregnancies will be expeditiously reported, if required by the local regulations.
- All suspected USADEs will be expeditiously reported to the US Food and Drug Administration (FDA) and the US Institutional Review Boards.
- All incidents occurring in Canada will be expeditiously reported to Health Canada.

All device deficiencies are to be recorded in the appropriate electronic CRF.

13.1.4 Anticipated Adverse Device Effects

The ADEs anticipated with the administration of Gelesis100 in overweight or obese subjects include nausea, dyspepsia (heartburn), abdominal distension (bloating), flatulence, abdominal pain, diarrhea, defecation urgency, and constipation. These AEs

were observed in the FLOW study. A comprehensive list of anticipated ADEs is provided in the Investigator's Brochure (8).

13.1.5 Risk Analysis

The Sponsor has established and maintains a process for identifying hazards associated with the use of its products, estimating, evaluating, controlling these risks and monitoring the effectiveness of the control. Detailed information regarding risk analysis is available in the Investigator's Brochure (8).

13.1.6 Precautions to Minimize Risk

To minimize technical and medical complications, the investigational medical device should be used only as instructed in the Clinical Investigation Plan. This includes:
- administering the prescribed amount of medical device before lunch and dinner (3 capsules)
- drinking the prescribed volume of water (approximately 100 mL + 500 mL) at the prescribed timing before meal
- consuming food at the prescribed timing (20 to 30 min after medical device administration)

13.2 Pregnancy

In case of pregnancy, the investigational medical device use must be discontinued and the Sponsor informed. Every effort should be made to follow up the pregnancy until its outcome is available.

The Contract Research Organization (CRO) Clinical Safety will provide the Investigator with the Pregnancy Reporting Form for completion. If the pregnancy is to be terminated, the anticipated date of termination should be provided.

13.3 Responsibilities for Adverse Event and Pregnancy Reporting

13.3.1 Responsibilities of the Investigator

- to inform the Sponsor about all AEs
- to inform the Sponsor about all SAEs, newly discovered pregnancies or pregnancy outcomes, within 24 h of awareness of the events, by:
  - entering the information about the event into the electronic CRF
  - in case the Investigator does not receive an automatic notification from the electronic CRF system of successful SAE submission or electronic CRF data entering is not possible:
    - printing the completed section of the electronic CRF (or in case completion of electronic CRF is not possible, completion of paper SAE form)
    - signing the completed SAE form

- sending the scanned SAE form by e-mail to the CRO Clinical Safety at pharmacovigilance@easthorn.eu (or in case sending a scan is not possible, faxing it to the CRO Clinical Safety at +420 244 462 271)

- to inform the Sponsor about all device deficiencies
- to make every effort to follow up the subject to a satisfactory resolution of the safety event or until the end of the study
- to respond to follow-up requests from the Sponsor/CRO Clinical Safety

13.3.2 Responsibilities of the Sponsor

- to ensure that:
  - all AEs are recorded and reviewed with the Investigators
  - all SAEs are reported to the relevant European Regulatory Authorities/Ethics Committees as required by the local regulations
  - all newly discovered pregnancies are reported as required by the local regulations
  - all suspected USADEs are reported to the FDA/Institutional Review Boards as required by the US regulations
  - all SADEs/incidents are reported to Health Canada as required by the Canadian regulations
  - all device deficiencies are recorded and reviewed with the Investigators
- during the course of the study, inform in writing all Investigators about all SAEs occurring at any of the participating sites
- to collect and maintain records of all AEs, device deficiencies, and pregnancies

14. TREATMENT/STUDY DISCONTINUATION

14.1 Temporary Treatment Discontinuation

The subjects may discontinue the study treatment for a period not exceeding 3 days for a valid medical reason, at the discretion of the Investigator.

14.2 Permanent Treatment/Study Discontinuation

14.2.1 Reasons

The subject may withdraw from the treatment with the investigational product (and the study) at any time and irrespective of the reason.

The Investigator will discontinue the investigational product (and the study) for the following reasons (after assessing their clinical relevance):

- contraception cessation
- pregnancy or wish of pregnancy
- significant intolerance to the study product
- an increase of ≥ 0.5% point (≥ 5.5 mmol/mol) in HbA1c from Baseline Visit in subjects with treated or untreated type 2 diabetes, or any increase if the new value falls in the

range of the exclusion criteria for HbA1c (see Section 8.4) after confirmation following a re-check at the next study visit (or before)
- an increase of ≥ 10% in total cholesterol, LDL cholesterol, or triglycerides from Baseline Visit in subjects with elevated lipids at Baseline Visit, or any increase if the new values fall in the range of the exclusion criteria for lipids (see Section 8.4) after confirmation following a re-check at the next study visit (or before)
- an increase of ≥ 10 mm Hg in supine SBP and/or supine DBP from Baseline Visit in subjects with treated or untreated hypertension, or any increase if the new values fall in the range of the exclusion criteria for blood pressure (see Section 8.4) after confirmation following a re-check at the next study visit (or before), based on the mean of two consecutive readings
- poor subject compliance with the study procedures and recommendations and/or major protocol deviation
- it is the best interest of the subject (including the need to add prohibited medications)

The subject is withdrawn from the treatment and the study if the treatment arm is unblinded for emergency reasons (see Section 15.5.4.2) or for a reason other than the interim analysis before the end of the treatment.

14.2.2 Procedures

When confirmed, a permanent treatment/study discontinuation should be recorded by the Investigator in the appropriate electronic CRF and, if applicable, reported to the relevant Ethics Committee/Institutional Review Board.

Every effort should be made to complete the clinical and laboratory evaluations required for Visits 12 and 13 as soon as possible (combined assessments).

Subjects who have withdrawn from the treatment/study cannot be re-enrolled in the study. Their screening number and randomization number must not be re-used.

15. STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as randomization, stratification, statistical power, and sample size. There will also be a brief discussion on analysis methodology, as well as some data conventions. The detailed descriptions of statistical analysis methods and data conventions will be in a separate document, the Statistical Analysis Plan (SAP). Any post-hoc analyses will be identified in the final Clinical Study Report.

15.1 Treatment Arms

The following treatment arms will be assessed:
- active: Gelesis100 2.25 g, twice daily
- placebo: matching placebo containing sucrose, twice daily

15.2 Baseline and Visit Windows

Baseline for a given parameter or endpoint is defined to be the last observation (obtained at either the Screening or Baseline Visit) taken before the first study product administration. The study visits and visit windows are Days 8 ± 2, 15 ± 2, 29 ± 2, 43 ± 2, 57 ± 2, 71 ± 2, 85 ± 2, 113 ± 3, 141 ± 3, 169 ± 3, 171, and 197 ± 3.

15.3 Description of Study Endpoints

The details of the study endpoints are presented in Section 11.

15.4 Sample Size Determination and Rationale

For this clinical trial, a total of 460 subjects (230 per arm) will be randomized to have 322 subjects complete the study (161 per arm) due to an anticipated dropout rate of 30%. This sample size will allow establishing both super-superiority and superiority with sufficient statistical power based on the primary endpoint of change in body weight from baseline.

The sample size calculation, using PASS (16), is based on the assumption that there will be a clinically meaningful difference of at least 3.0% weight loss between the two arms after 24 weeks of treatment. This 3.0% is also being used as margin to establish the super-superiority (lower bound of the confidence interval of Gelesis100 effect ≥ 3.0% of placebo effect). With the above sample size, there is 85% statistical power for a 3.0% margin super-superiority (i.e., delta of at least 4.5%) with a common SD of 5.0% and a type I error rate of 0.05 (one-sided test). The statistical formula for the study hypothesis is as follows:

H_0: $\mu_{placebo} - \mu_{Gelesis100} < 3.0\%$

H_A: $\mu_{placebo} - \mu_{Gelesis100} \geq 3.0\%$

Where $\mu_{placebo}$ is the mean percent change from baseline in the placebo arm and $\mu_{Gelesis100}$ is the mean percent change from baseline in the Gelesis100 arm.

In addition, with the above sample size, there will be at least 90% statistical power to establish that the difference between the two arms is greater than 0 (i.e., the superiority with no margin), with a common SD of 5.0% and a type I error rate of 0.05 (two-sided tests), with the null hypothesis that the mean percent change from baseline in primary effectiveness endpoint is the same for both treatment arms and the alternative hypothesis that the Gelesis100 arm provides a different mean percent change in body weight than does the placebo arm. The statistical formula for the study hypothesis is as follows:

H_0: $\mu_{placebo} - \mu_{Gelesis100} = 0$

H_A: $\mu_{placebo} - \mu_{Gelesis100} \neq 0$

Where $\mu_{placebo}$ is the mean percent change from baseline in the placebo arm and $\mu_{Gelesis100}$ is the mean percent change from baseline in the Gelesis100 arm.

15.5 Randomization, Stratification, Blinding, and Unblinding

15.5.1 Randomization

This is a multicenter randomized clinical trial with sites from different countries (US, Canada, and several European countries). Eligible subjects will be randomly assigned to the active arm or the placebo arm based on a randomization schedule. An individual independent of the clinical trial team will develop the randomization schedule.

The randomization will be central and will use mixed blocks of 2 and 4 with a 1:1 ratio of active to placebo to ensure even distribution of active and placebo subjects. Each arm will include approximately 230 subjects.

The randomization assignment will be made through an interactive web randomization system maintained by the CRO. The site representative will log into the eClinical system (developed by Clinical Research Technology, Srl.) and enter the information pertaining to the subject to be randomized, and will be notified of the next sequential randomized treatment.

15.5.2 Stratification

The following characteristics at the Screening Visit will be used as stratification factors at the time of randomization and the centralized randomization procedure will balance treatment arm assignments in each country or combination of countries for the following stratification factors:
- male, BMI < 35, and normal fasting glucose
- male, BMI < 35, and impaired/diabetic fasting glucose
- male, BMI ≥ 35, and normal fasting glucose
- male, BMI ≥ 35, and impaired/diabetic fasting glucose
- female, BMI < 35, and normal fasting glucose
- female, BMI < 35, and impaired/diabetic fasting glucose
- female, BMI ≥ 35, and normal fasting glucose
- female, BMI ≥ 35, and impaired/diabetic fasting glucose

The selection of these stratification factors is based on the facts that gastric capacity has a tendency to be higher in male subjects and in subjects with higher BMI, and weight loss can be more important in subjects with higher fasting glucose (data from the FLOW study).

15.5.3 Blinding

As this is a double-blind trial, the study participants, the Investigators, all other study site personnel, the Monitoring Team involved in collecting the data, the Data Management Team involved in querying the clinical sites, and the Sponsor will be blinded to treatment assigned to the subject during the entire course of the study. Placebo capsules matching

the size, shape, color, and coating of Gelesis100 will be used for blinding the study treatment.

The randomization lists containing the assignment of subjects to treatment arms will be securely provided to the person involved in randomizing the subjects (i.e., the WebMaster), who has no role in screening, qualifying, enrolling, or evaluating study subjects. No other study personnel other than the WebMaster and the randomization code generator will have access to the randomization codes for the study.

15.5.4 Unblinding

To maintain the study blind, treatment unblinding will occur only per the cases specified below. The unblinding will be performed after all clinical data have been received, data inconsistencies have been resolved, and the database has been locked, except for the case of the interim analysis by an independent statistician and the emergency unblinding including management of a suspected USADE/SADE.

15.5.4.1 Unblinding for Interim Analysis

An interim analysis is planned to be conducted when approximately 50% of the subjects have been randomized and completed Visit 13 (Week 24) or early terminated, whichever comes first. The details of this interim analysis are presented in Section 15.6.

Unblinded treatment assignments for the interim analysis will only be given to the independent statistician. For this analysis, there will be no subject level unblinding to any other personnel in the study except the WebMaster and the randomization code generator. The summary tables will be unblinded to the treatment arm level and will be presented using masked treatment arms. Unblinding of treatment arms to the Data Monitoring Committee members will only occur per their request.

15.5.4.2 Unblinding for Emergency

Every attempt will be made to maintain the blind throughout the study. Breaking the blind prematurely will be allowed only under two circumstances:
- when knowledge of the treatment assignment is essential for treating a subject in case of an emergency
- as part of the management of a suspected USADE/SADE

The unblinding of treatment assignment will be performed by:

The Investigator in case of a suspected SADE if:

- The information about the treatment assignment is essential for the subsequent treatment of the suspected SADE.

Should the need for unblinding the code arise, the Sponsor's Trial Monitor must be contacted immediately via phone and e-mail to approve the unblinding. This prior approval can be waived if there is a life-threatening situation requiring immediate

intervention. However, the Investigator must notify the Sponsor (or designee) as soon as possible following the unblinding event.

The CRO Clinical Safety in case of a suspected USADE/SADE if:

- The Regulatory Authorities/Ethics Committee/Institutional Review Board request the information about the treatment assignment.
- The Sponsor needs the information about the treatment assignment for the evaluation of risk analysis.

The CRO Clinical Safety performs such unblinding upon approval from the Sponsor. After unblinding, the CRO Clinical Safety Manager informs both the Sponsor and the Investigator about the study subject in question.

The unblinding is performed by logging onto the eClinical system and entering the appropriate subject-specific information. The user will follow the prompts for emergency unblinding and will be notified of the treatment assignment on the screen. The date and reason for revealing the treatment assignment for the subjects will be captured in the eClinical system. Sponsor and CRO Clinical Safety will be notified of the unblinding. Sponsor's Trial Monitor will follow up with the site in a case the site did not obtain prior approval to unblind.

Subjects who are unblinded for emergency reasons will be discontinued from the treatment.

15.5.4.3 Unblinding for Final Analysis

Treatment unblinding and release of the randomization codes of the investigational product assignments for the study will occur if the trial is terminated or, at the time of database lock. That is after all randomized subjects have completed the study or discontinued from the study and all clinical data have been received and data inconsistencies have been resolved.

15.6 Interim Analysis

An interim analysis will be conducted when approximately 50% of subjects have been randomized and completed Visit 13 (Week 24) or early terminated, whichever comes first.

The procedures for this interim analysis will be based on a standard operating procedure that has a well-established firewall to protect the integrity of the trial. The interim analysis will be performed by an independent statistician, who is not otherwise associated with the conduct of this trial.

The main purpose of this interim analysis is to assess:
- sample size re-assessment to evaluate the sample size estimations, which will serve in the planning of the remainder of the study
- other parameters that the Data Monitoring Committee may request

15.6.1 Procedures for Interim Analysis

- Cutoff dates for collection of electronic CRFs, data querying, database lock, and analysis are established based on an estimated target date of the approximately 50% of subject completing 24 weeks of treatment or early terminated.
- All data available by the cutoff date is entered, validated, queries generated and resolved or pending queries documented.
- The database is locked.
- The locked database is saved in a drive to which only the independent statistician responsible for the interim analysis has access.

Using the data obtained in this interim analysis, the independent statistician will prepare safety summaries and calculate the following metrics for the primary endpoint:

- Mean percent change at Week 24, the SD and the observed number of subjects in the active arm.
- Mean percent change at Week 24, the SD and the observed number of subjects in the placebo arm.
- The dropout rate at the time of the interim analysis for both arms.
- The conditional power (CP) analysis of the study at the time of the interim analysis (17) (the method for this calculation is provided in below).
- The revised sample size requirement based on this interim analysis (18) (the rule and method for sample size recalculation are provided below).

15.6.2 Conditional Power Calculation

The CP will be calculated according to the below formula using the mean percent changes in the active arm compared to placebo arm:

$CP(f_1, z_1) = \Phi\{z_1/\sqrt{f_1(1-f_1)} - z_\alpha/\sqrt{(1-f_1)}\}$
where:

- CP (f_1, z_1) is the CP at the interim analysis
- $\Phi\{.\}$ is the cumulative distribution function of a standard normal distribution ($\mu = 0$, $\sigma^2 = 1$)
- f_1 is the fraction of subjects enrolled and used in the interim analysis before decision of increasing the sample size
- z_α is the upper α quintile for standard normal distribution
- z_1 is the standardized normal, the z score will be obtained from the following formula:

  $z_1 = (\mu_a - \mu_c - 3)/\sqrt{[\sigma_a 2/n_a + \sigma_c 2/n_c]}$
  where:

  - μ_a = the mean percent changes at Week 24 for the subjects in the active arm

- μ_c = the mean percent changes at Week 24 for the subjects in the placebo arm
- σ_a = the SD of percent changes at Week 24 for the subjects in the active arm
- σ_c = the SD of percent changes at Week 24 for the subjects in the placebo arm
- n_a = the number of subjects in the active arm used in the interim analysis
- n_c = the number of subjects in the placebo arm used in the interim analysis
- a = the active arm
- c = the placebo arm

The resulting CP will be used to determine whether the sample size should be increased or remain unchanged.

15.6.3 Rule and Method for Increasing Sample Size

- If the CP < 36%, the sample size will not be increased and the study will continue as is.
- If the CP is ≥ 36% and < 85%, the sample size may be adjusted to retain the original power of 85%.
- If the CP is ≥ 85%, the study will continue as is.

Regardless of the size of the CP, the study sample size will not be reduced.

15.6.4 Data Provided to Data Monitoring Committee

The Data Monitoring Committee will receive a statistical report. The details on the content of the report will be described in the Data Monitoring Committee charter.

15.6.5 Stopping Rule

The study will not be stopped for overwhelming effectiveness reasons. However, the Data Monitoring Committee may recommend stopping the study for safety reasons at any time during the trial. The Investigator may decide to stop the study for reasons described in Section 14.2.1. The Sponsor may also decide to stop the study for safety or other reasons at any time during the trial (see Section 22.1).

15.6.6 Stopping Rule Provided to Sponsor by Data Monitoring Committee

The Data Monitoring Committee will make recommendations to the Sponsor on the sample size adjustment and any safety concerns.

15.6.7 Type I Error Rate Adjustment

There will be no type I error rate adjustment as there is no intention to stop the study for effectiveness benefit. In addition, the sample size is planned to be increased when the interim CP is promising and this will protect the type 1 error rate (18).

15.7 General Statistical Considerations

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.3 or later. Descriptive statistics (number of observations, mean, SD, median, minimum, and maximum values) will be calculated by treatment arm for continuous variables. Frequencies and percentages will be presented by treatment arm for categorical variables.

15.7.1 Analysis Populations

15.7.1.1 Intention-to Treat Population

The ITT population is defined as all randomized subjects.

15.7.1.2 Per Protocol Population

The per protocol (PP) population refers to all randomized subjects who were successfully randomized, treated, and stayed on their assigned treatment with no major protocol deviation.

15.7.1.3 Safety Population

The safety population is defined as any subject receiving the treatment after randomization. This population will be used for the analysis of safety parameters.

15.7.2 Covariates

For effectiveness analyses, the stratification factors and the respective baseline values for the endpoint will be used as covariates in the analysis models.

15.7.3 Missing Data

For effectiveness evaluation, missing data points will be imputed using multiple imputation approach. This approach is robust and the least biased for the missing at random cases. This method will be detailed in the SAP.

15.7.4 Multiple Comparisons and Multiplicity

For the co-primary endpoints, there will be no type I error adjustment.

For the secondary endpoints, the Closed Test procedure will be used. All the secondary endpoints will be ordered prior to database lock and tested according to the order.

15.7.5 Subgroup Analysis

Several subgroup analyses will be conducted for the stratification factors as well as the pre-specified secondary endpoints. Subgroup analyses will also be performed based on the results of serum amylase and genomic tests. The detail of these subgroup analyses will be presented in the SAP.

15.8 Statistical Methods

A SAP will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the effectiveness and safety data from this trial.

All the effectiveness endpoints presented here will be conducted using both the ITT and the PP populations. All safety analyses will be conducted using the safety population.

All data collected will be summarized according to the variable type:

- Continuous data summaries will include:
    - Number of observations, mean, SD, median, minimum, and maximum values
    - ANCOVA with the stratification factors and the respective baseline values for the endpoint in the model for inferential statistics
- Categorical data summaries will include:
    - Frequency counts and percentages
    - Logit model with the stratification factors and the respective baseline values for the endpoint in the model for inferential statistics
- Time-dependent data:
    - Cox proportional hazards model will be used to analyze time-dependent data
    - Kaplan-Meier will be used to depict the time to event data

15.8.1 Subject Disposition

The disposition of all subjects who sign an Informed Consent Form will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations will be summarized by treatment arm. Disposition and reasons for study discontinuation will also be provided as a by-subject listing.

15.8.2 Demographics and Baseline Characteristics Analysis

Demographic and baseline characteristic data will be summarized descriptively and/or presented as a by-subject listing for the safety population. In addition, all the known potential risk factors (e.g., diabetes, dyslipidemia, hypertension) will be tabulated and compared between the two treatment arms.

15.8.3 Extent of Exposure to Study Product

Extent of exposure to the study product will be summarized for each arm.

15.8.4 Compliance with Diet, Life-Style, and Study Product

Compliance with the diet and life-style recommendations and the intake of the study product will be summarized for each arm.

15.8.5 Concomitant Medications/Therapies

Concomitant medications/therapies will be summarized separately for the safety population. All prior and concomitant medications recorded in the electronic CRF will be coded to all matching Anatomic Therapeutic Classification codes using the most recent version of WHO Drug version. Descriptive summaries, by treatment arm, will be prepared using the coded term. All concomitant medications/therapies recorded in the electronic CRF will be listed.

15.8.6 Effectiveness Analysis

15.8.6.1 Primary Analysis

The primary analysis will be conducted on the ITT population.

Co-primary endpoints

ANCOVA will be used to compare the percent change in weight from baseline to Day 171 for the two treatment arms. The stratification factors and baseline weight will be included in the analysis and associated treatment difference, 95% confidence interval around the difference and *P* value for the treatment effect will be reported.

The proportion of body weight responders will be presented descriptively by treatment arm. Responders in this case will be defined as those subjects who have achieved ≥ 5% reduction in body weight compared to baseline. In addition, the Logit model will be used to analyze the percent of responders, with the stratification factors and baseline weight in the model.

To maintain the trial-wise type I error rate at 0.05, a closed test procedure will be used for the secondary and tertiary endpoints. The order of the endpoints will be as follows:

Secondary and tertiary endpoints
Analysis of the secondary and tertiary endpoints will be summarized according to the variable type:
- continuous data summaries will be based on ANCOVA or Mixed Model using the stratification factors and the respective baseline values for the endpoint as a covariate in the model
- categorical data summaries will be based on Logit model using the stratification factors and the respective baseline values for the endpoint as a covariate in the model

15.8.6.2 Supportive Analysis
To assess the consistency of the primary analysis results, supportive analysis will be conducted using the PP population. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population used. The PP population will be used for the supportive analysis while ITT population will be used for the primary analysis.

15.8.6.3 Longitudinal Analysis
Longitudinal data analyses will be conducted for selected endpoints; these will be pre-specified in the SAP.

15.8.7 Safety Assessments

15.8.7.1 Adverse Events
All AEs will be presented by number of episodes and by number of subjects experiencing the event in each arm with information on time of occurrence and duration.

AEs (including ADEs) will be coded using the latest version of MedDRA. Treatment-emergent AEs (TEAEs) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment arm, System Organ Class, and Preferred Term. The following TEAEs summaries will be provided:
- TEAEs by severity grade
- TEAEs by relationship to study treatment

In addition, separate summaries of SAEs (SADEs) and AEs (ADEs) resulting in discontinuation of study treatment will be presented.

15.8.7.2 Physical Examination
All physical examination clinically significant abnormal findings will be listed.

15.8.7.3 Vital Signs
All data from the vital signs assessments (blood pressure, heart rate) will be listed. The data will also be summarized and presented by treatment arm and timepoint.

15.8.7.4 Laboratory Tests

All laboratory values and their changes from baseline will be listed. Laboratory measurements will also be summarized as continuous variable and presented by treatment arm and timepoint.

16. STUDY COMMITTEES

16.1 Steering Committee

To ensure the proper scientific completion of the study, a Steering Committee (Research Coordination Committee) will be established. The Committee will have 7 members. The Sponsor and the Principal Investigator will nominate 6 members for this Committee (2 members from the Sponsor, 4 members from the investigational sites). An additional member will be nominated from the Monitoring Team of the CRO.

The Steering Committee should follow the overall progress of the study, ensure smooth communication, seek to solve any unforeseen events affecting the study, and monitor the progress of the results. The Steering Committee will remain blinded throughout the study.

16.2 Data Monitoring Committee

To ensure the proper safety of the study, a Data Monitoring Committee will be established. The Committee will have 3 members (1 Chairman, 1 Clinical Investigator, and 1 Statistician).

The responsibilities of the Data Monitoring Committee will be detailed in a charter.

17. ETHICAL CONSIDERATIONS

17.1 Principles

The study will be conducted in accordance with the principles established by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments established by the World Medical Assemblies and the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practices (GCP), and in compliance with European Norm (EN) International Organization for Standardization (ISO) 14155:2011.

17.2 Informed Consent

The Investigator (or a designated representative) should fully inform the subject of all relevant aspects of the study. Prior to the study start, the written Informed Consent Form must be dated and signed by the subject and by the person who conducted the informed consent discussion. The Informed Consent Form will be translated to the state language of the country where the trial will be conducted in accordance with language requirements in US, Canada, and the EEA [status: 1/2007]. The subject will receive the

original or the copy of the translated, dated, and signed Informed Consent Form. Any new significant findings will be communicated to the subject.

17.3 Ethics Committee/Institutional Review Board

The Investigator must submit this Clinical Investigation Plan (together with the Informed Consent Form, the Investigator's Brochure, the Investigator's curriculum vitae, and any other relevant document) to the appropriate Ethics Committee/Institutional Review Board after the approval by the Sponsor, and is required to forward to the Sponsor a copy of the written and dated favorable opinion signed by the Chairman of the Ethics Committee/Institutional Review Board with information on the composition of the Committee/Board. The investigational product will not be released at the study site and the study will not start until this copy has been received by the Sponsor.

Submission in Europe can be done by the Investigator or the Sponsor (or designee).

Responsibility for coordinating with Ethics Committee/Institutional Review Board is defined in the Investigator/Sponsor (CRO) Contract.

During the course of the study, any amendment to the Clinical Investigation Plan or any update to the Investigator's Brochure will be sent to the Ethics Committee/Institutional Review Board. Any revision to the Clinical Investigation Plan or the Informed Consent Form must be approved by the Ethics Committee/Institutional Review Board prior to implementation, unless there is a safety issue for the study subject.

Any additional requirements imposed by the Regulatory Authorities or the Ethics Committee/Institutional Review Board should be followed.

If requested, a summary of the study outcome will be sent to the Ethics Committee/Institutional Review Board at the end of the trial.

17.4 Confidentiality

All information provided by the Sponsor or produced during the study is confidential. The Investigator and the Sub-Investigators agree to keep this information confidential and not to disclose it to any third party without the prior written approval of the Sponsor. The Ethics Committee/Institutional Review Board members have also the same obligation of confidentiality.

18. ADMINISTRATIVE AND REGULATORY PROCEDURES

18.1 Laws

The study will be conducted in compliance with laws, regulations, and guidelines of the countries where the study is conducted (US, Canada, Europe).

18.2 Clinical Trials Registration

This trial will be registered in appropriate clinical trial database(s) consistent with federal law and regulation, FDA guidance, and WHO mandate.

18.3 Curriculum Vitae

An updated copy of the curriculum vitae of the Investigator and the Sub-Investigators will be provided to the Sponsor prior to the start of the study.

18.4 Record Retention

The Investigator must maintain confidential all study documentation and prevent accidental or premature destruction of the documents.

The documents should be retained at least 15 years after the completion of the study. If archiving can no longer be ensured by the Investigator, the Sponsor should be informed and a mutually agreed upon alternative should be proposed. The Investigator must notify the Sponsor prior to destroying any document before the 15-year period.

18.5 Data Protection

The Sponsor should treat the subject's personal data and the Investigator's personal data in compliance with all applicable laws and regulations, and take all appropriate measures to protect the data and prevent access to the data by an unauthorized third party.

18.6 Insurance

The Sponsor certifies that it has a liability insurance policy covering the subjects and the liability of the Investigator and Sub-Investigators. The insurance policy is in accordance with local laws and requirements.

The insurance of the Sponsor does not relieve the Investigator and Sub-Investigators of any obligation to maintain their own liability insurance policy as required by applicable law.

18.7 Financial Arrangements

The sponsor is providing financial support and material through contracts with sites participating in the study. Study subjects may be provided reimbursement for reasonable travel expenses and accommodation associated with the completion of study visits, when appropriate under local regulation.

19. CLINICAL INVESTIGATION PLAN AMENDMENTS

Any amendment to the Clinical Investigation Plan requires a written favorable opinion from the Ethics Committee/Institutional Review Board prior to its implementation, unless there are overriding safety reasons. In case a change to the Informed Consent Form becomes necessary following the amendment, the Investigator must receive a favorable opinion from the Ethics Committee/Institutional Review Board prior to the implementation of the change.

20. CLINICAL INVESTIGATION PLAN DEVIATIONS

A Clinical Investigation Plan deviation (protocol deviation) is any change or alteration to the procedures stated in the Clinical Investigation Plan, Informed Consent Form, study materials (e.g., questionnaires), or recruitment process originally approved by the Ethics Committee/Institutional Review Board.

Major protocol deviation is any intentional or unintentional change from the approved Clinical Investigation Plan that adversely affects the risk/benefit ratio of the study, the rights, safety, or welfare of the study subjects or others, or the integrity of the study (ability to draw conclusions from the study data), such as any deviation from subject inclusion and exclusion criteria or subject informed consent procedures, study medication dispensing error, etc.

Minor protocol deviation is any deviation that does not have the potential to negatively impact the willingness of the subjects to participate in the study, the safety of the study subjects, or the integrity of study, such as incomplete/inadequate subject testing procedures, non-compliance with medication regimens, visits performed outside of specified visit windows, etc.

The Investigator is not allowed to deviate from the Clinical Investigation Plan except under emergency circumstances to protect rights, safety, and well-being of the study subjects.

All protocol deviations are to be reported to the Sponsor. Major protocol deviations are to be reported according to local regulations.

21. STUDY MONITORING

21.1 Responsibilities of the Sponsor

The Sponsor is responsible to Regulatory Authorities for ensuring the proper conduct of the study (ethical aspects, compliance, integrity and validity of the data recorded). The main duty of the Monitoring Team is to help the Sponsor (and the Investigator) to achieve this objective. A Monitoring Plan will be prepared before the start of the study. During the study, the Monitoring Team will contact the site at regular intervals (by monitoring visits, phone calls, e-mails, letters, or fax) to review the study progress and

discuss any relevant issue. The Monitoring Team must check the electronic CRF entries against the source documents.

21.2 Responsibilities of the Investigator

The Investigator should accept and sign the Clinical Investigation Plan. The Investigator is responsible to conduct the study in accordance with the Clinical Investigation Plan, the ICH guidelines for GCP, the EN ISO 14155:2011, and the applicable regulatory requirements. The Sub-Investigators appointed to assist the Investigator will be under direct responsibility of the Investigator. The Investigator agrees to provide reliable data as requested by the Clinical Investigation Plan (through electronic CRF and query) in an accurate and legible manner and to ensure direct access to source documents to the Sponsor's representatives.

22. PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

22.1 Decided by the Sponsor

The Sponsor may decide to discontinue the study or to close the site for the following reasons:
- the number of subjects who have completed the study is considered sufficient
- the Sponsor has information on the investigational product leading to a doubt about the benefit/risk ratio
- the aim of the study is no longer of interest
- the Investigator has not included sufficient number of subjects in the study after a reasonable period of time mutually agreed upon
- the presence of breach by the Investigator of a fundamental obligation

The Sponsor must notify the Investigator in writing and also inform the Regulatory Authorities and the Ethics Committee/Institutional Review Board.

22.2 Decided by the Investigator

The Investigator must notify the Sponsor (prior notice of 30 days) of this decision and give the reason in writing. The Regulatory Authorities and the Ethics Committee/Institutional Review Board should also be informed.

The Regulatory Authorities or the Ethics Committee/Institutional Review Board may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible.

The Investigator or authorized designee should promptly inform the enrolled subjects at the site in case of discontinuation/termination of the study.

23. PROPERTY RIGHTS

All information, documents, and investigational product provided by the Sponsor remain the property of the Sponsor. All the results arising from the study remain the property of the Sponsor.

All inventions, formulations, and discoveries that are developed, conceived, and/or made by the CRO and/or the Investigator based on confidential information received from the Sponsor and that are specific to programs, projects, and/or products of the Sponsor will be the sole and exclusive property of the Sponsor.

24. COMMUNICATION AND PUBLICATION OF RESULTS

The Sponsor has the right to communicate and publish the results of the study at any time by proposing authorship to relevant authors from the Investigator's Team. The Investigator has the right to communicate and publish the results of the study by proposing authorship to relevant authors from the Sponsor's Team and after obtaining written approval of the manuscript from the Sponsor. The results of the study will be submitted for presentation at scientific meetings and/or publication in scientific journals. The Sponsor has the right to postpone a presentation/publication for a period not exceeding 18 months after the availability of the study results.

25. QUALITY ASSURANCE AUDITS AND REGULATORY INSPECTIONS

The Clinical Trial described in this Clinical Investigation Plan will be subject to Quality Assurance evaluations in order to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with the ICH E6 GCP principles, EN ISO 14155:2011, and the applicable regulatory requirements. The Investigator may be audited by the Sponsor's Quality Assurance Auditor periodically in accordance with Clinical Quality Assurance audit plan. The audit plan will be discussed by the Sponsor and the Investigator. The Investigator agrees to allow the auditors to have direct access to the study records for review. The confidentiality of the data audited should be respected by all parties. The Investigator should immediately inform the Sponsor about the planned audit and the outcome of the audit by the Regulatory Authorities. Corrective actions should be implemented for all problems found during the audit.

The Investigator agrees to allow direct access to source data/documents, including subject journals, during monitoring, auditing and/or inspection by the Regulatory Authorities and the Ethics Committee/Institutional Review Board.

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27. APPENDICES

27.1 Appendix 1: Binge Eating Disorder

QUESTIONNAIRE ON EATING AND WEIGHT PATTERNS-REVISED (QEWP-R) – ABBREVIATED VERSION

Last Name _____ First Name _____ M.I. _____

Subject Number _____ Date _____

Thank you for completing this questionnaire. Please circle the appropriate number or response, or write in information where asked. You may skip any question you do not wish to answer.

1. Age _____ years
2. Sex: 1 Male 2 Female
3. What is your ethnic/racial background?
    1. Black (not Hispanic)
    2. Hispanic
    3. White (not Hispanic)
    4. Asian
    5. Other (please specify)

       _____
4. How far did you get in school?
    1. Grammar school, junior high school or less
    2. Some high school
    3. High school graduate or equivalency (GED)
    4. Some college or associate degree
    5. Completed college
5. How tall are you?

   _____ cm (in)
6. How much do you weigh now?

   _____ kg (lbs)

7. What has been your highest weight ever (when not pregnant)?

   _____ kg (lbs)

8. Have you ever been overweight by at least 4.5 kg (10 lbs) as a child or 6.8 kg (15 lbs) as an adult (when not pregnant)?

   1 Yes 2 No or not sure

IF YES: How old were you when you were first overweight (at least 4.5 kg (10 lbs) as a child or 6.8 kg (15 lbs) as an adult)? If you are not sure, what is your best guess?

_____ years

9. How many times (approximately) have you lost 9 kg (20 lbs) or more – when you weren't sick – and then gained it back?
   1. Never
   2. Once or twice
   3. Three or four times
   4. Five times or more

10. During the past six months, did you often eat within any two-hour period what most people would regard as an unusually large amount of food?

    1 Yes 2 No

IF NO: SKIP TO QUESTION 15

11. During the times when you ate this way, did you often feel you couldn't stop eating or control what or how much you were eating?

    1 Yes 2 No

IF NO: SKIP TO QUESTION 15

12. During the past six months, how often, on average, did you have times when you ate this way – that is, large amounts of food plus the feeling that your eating was out of control? (There may have been some weeks when it was not present – just average those in).
    1. Less than one day a week
    2. One day a week
    3. Two or three days a week
    4. Four or five days a week
    5. Nearly every day

13. Did you usually have any of the following experiences during these occasions?
    a. Eating much more rapidly than usual? Yes No
    b. Eating until you felt uncomfortably full? Yes No
    c. Eating large amounts of food when you didn't feel physically hungry? Yes No
    d. Eating alone because you were embarrassed by how much you were eating? Yes No
    e. Feeling disgusted with yourself, depressed, or feeling very guilty after overeating? Yes No

14. Think about a typical time when you ate this way – that is, large amounts of food plus the feeling that your eating was out of control.
    a. What time of day did the episode start?
        1. Morning (8 am to 12 noon)
        2. Early afternoon (12 noon to 4 pm)
        3. Late afternoon (4 pm to 7 pm)
        4. Evening (7 pm to 10 pm)
        5. Night (after 10 pm)

    b. Approximately how long did this episode of eating last, from the time you started to eat to when you stopped and didn't eat again for at least two hours

       _____ hours _____ minutes

    c. As best you can remember, please list everything you might have eaten or drunk during that episode. If you ate for more than two hours, describe the foods eaten and liquids drunk during the two hours that you ate the most. Be specific – include brand names where possible and amounts as best you can estimate. (For example: 198 g (7 oz) Ruffles potato chips; 1 cup Breyer's chocolate ice cream with 2 teaspoons hot fudge; two 237-mL (8-fl oz) glasses of Coca-cola, 1½ ham and cheese sandwiches with mustard).

       _____

       _____

       _____

    d. At the time this episode started, how long had it been since you had previously finished eating a meal or snack?

       _____ hours _____ minutes

15. In general, during the past six months, how upset were you by overeating (eating more than you think is best for you)?
    1. Not at all
    2. Slightly
    3. Moderately
    4. Greatly
    5. Extremely

16. In general, during the past six months, how upset were you by the feeling that you couldn't stop eating or control what or how much you were eating?
    1. Not at all
    2. Slightly
    3. Moderately
    4. Greatly
    5. Extremely

27.2 Appendix 2: Food Habits

QUESTIONNAIRE ON FOOD HABITS BEFORE TREATMENT

Last Name _____ First Name _____ M.I. _____

Subject Number _____ Date _____

Thank you for completing this questionnaire. Please circle the appropriate letter. You may skip any question you do not wish to answer.

1. Do you eat meat, like beef chicken or pork?
   a. Yes, every day or almost every day
   b. Yes, but not every day
   c. I hardly eat those foods
   d. I never eat those foods

2. Are you a vegetarian or a vegan?
   a. I am a vegetarian
   b. I am a vegan
   c. I am not a vegetarian or a vegan

3. Do you eat breakfast?
   a. Yes, every day
   b. Yes, but not every day
   c. Only once or twice a week
   d. I almost never eat breakfast

4. Which statement best describes your eating habits regarding main meals?
   a. I eat almost every day breakfast lunch and dinner
   b. I eat almost every day lunch and dinner but not breakfast
   c. I eat almost every day breakfast and lunch but not dinner
   d. I eat almost every day breakfast and dinner but not lunch
   e. I do not eat regular meals and I eat when I am hungry

5. Which statement best describes your eating habits regarding snacks?
   a. I usually do not eat much during the meals and I like to have snacks during the day
   b. I eat most of my food during the meals but I also have three or more snacks during the day
   c. I eat most of my food during the meals and I have not more than two snacks during the day
   d. I eat most of my food during the meals and I usually do not have snacks during the day

27.3 Appendix 3: Food Habits and Satisfaction

QUESTIONNAIRE ON FOOD HABITS AND SATISFACTION AFTER TREATMENT

Last Name _____ First Name _____ M.I. _____

Subject Number _____ Date _____

Thank you for completing this questionnaire. Please circle the appropriate letter or write in information where asked. You may skip any question you do not wish to answer.

Food Habits

1. Do you eat meat, like beef chicken or pork?
   a. Yes, every day or almost every day
   b. Yes, but not every day
   c. I hardly eat those foods
   d. I never eat those foods

2. Are you a vegetarian or a vegan?
   a. I am a vegetarian
   b. I am a vegan
   c. I am not a vegetarian or a vegan

3. Do you eat breakfast?
   a. Yes, every day
   b. Yes, but not every day
   c. Only once or twice a week
   d. I almost never eat breakfast

4. Which statement best describes your eating habits regarding main meals?
   a. I eat almost every day breakfast lunch and dinner
   b. I eat almost every day lunch and dinner but not breakfast
   c. I eat almost every day breakfast and lunch but not dinner
   d. I eat almost every day breakfast and dinner but not lunch
   e. I do not eat regular meals and I eat when I am hungry

5. Which statement best describes your eating habits regarding snacks?
   a. I usually do not eat much during the meals and I like to have snacks during the day
   b. I eat most of my food during the meals but I also have three or more snacks during the day
   c. I eat most of my food during the meals and I have not more than two snacks during the day
   d. I eat most of my food during the meals and I usually do not have snacks during the day

Satisfaction

1. Would you recommend these capsules to a relative or a friend who wants to lose weight?
   a. Yes
   b. No

2. On a scale of 1 to 10, how would you rate your experience using these capsules? (10 being very positive and 1 being very negative) ____

   Please explain why you gave this rating:

   _____

   What did you like about the capsules?

   _____

   What did you not like about the capsules?

   _____

3. Would you like to continue receiving these capsules?
   a. Yes
   b. No

   If No, please explain why:

   _____

4. If you were to continue taking the same amount of active product in this study, would you prefer to take smaller capsules but in a larger number? (Please see the real examples before answering the question)
   a. Yes, I would prefer smaller capsules, but more of them (e.g., 4 or 5 capsules each time)
   b. No, I would prefer the current size capsules and continue with 3 capsules each time

27.4 Appendix 4: Impact of Weight on Quality of Life

QUESTIONNAIRE ON IMPACT OF WEIGHT ON QUALITY OF LIFE (IWQOL)

Last Name _____ First Name _____ M.I. _____

Subject Number _____ Date _____

Impact of Weight on Quality of Life Questionnaire—Lite Version (IWQOL-Lite)

Please answer the following statements by circling the number that best applies to you in the past week. Be as open as possible. There are no right or wrong answers.

Physical Function		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble picking up objects.	5	4	3	2	1
2.	Because of my weight I have trouble tying my shoes.	5	4	3	2	1
3.	Because of my weight I have difficulty getting up from chairs.	5	4	3	2	1
4.	Because of my weight I have trouble using stairs.	5	4	3	2	1
5.	Because of my weight I have difficulty putting on or taking off my clothing.	5	4	3	2	1
6.	Because of my weight I have trouble with mobility.	5	4	3	2	1
7.	Because of my weight I have trouble crossing my legs.	5	4	3	2	1
8.	I feel short of breath with only mild exertion.	5	4	3	2	1
9.	I am troubled by painful or stiff joints.	5	4	3	2	1
10.	My ankles and lower legs are swollen at the end of the day.	5	4	3	2	1
11.	I am worried about my health.	5	4	3	2	1
Self-esteem		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I am self-conscious.	5	4	3	2	1
2.	Because of my weight my self-esteem is not what it could be.	5	4	3	2	1
3.	Because of my weight I feel unsure of myself.	5	4	3	2	1
4.	Because of my weight I don't like myself.	5	4	3	2	1
5.	Because of my weight I am afraid of being rejected.	5	4	3	2	1
6.	Because of my weight I avoid looking in mirrors or seeing myself in photographs.	5	4	3	2	1
7.	Because of my weight I am embarrassed to be seen in public places.	5	4	3	2	1

Sexual Life		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I do not enjoy sexual activity.	5	4	3	2	1
2.	Because of my weight I have little or no sexual desire.	5	4	3	2	1
3.	Because of my weight I have difficulty with sexual performance.	5	4	3	2	1
4.	Because of my weight I avoid sexual encounters whenever possible.	5	4	3	2	1

Public Distress		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I experience ridicule, teasing, or unwanted attention.	5	4	3	2	1
2.	Because of my weight I worry about fitting into seats in public places (e.g. theaters, restaurants, cars, or airplanes).	5	4	3	2	1
3.	Because of my weight I worry about fitting through aisles or turnstiles.	5	4	3	2	1
4.	Because of my weight I worry about finding chairs that are strong enough to hold my weight.	5	4	3	2	1
5.	Because of my weight I experience discrimination by others.	5	4	3	2	1
Work (Note: For homemakers and retirees, answer with respect to your daily activities.)		ALWAYS TRUE	USUALLY TRUE	SOMETIMES TRUE	RARELY TRUE	NEVER TRUE
1.	Because of my weight I have trouble getting things accomplished or meeting my responsibilities.	5	4	3	2	1
2.	Because of my weight I am less productive than I could be.	5	4	3	2	1
3.	Because of my weight I don't receive appropriate raises, promotions or recognition at work.	5	4	3	2	1
4.	Because of my weight I am afraid to go on job interviews.	5	4	3	2	1

27.5 Appendix 5: List of Source Data

Subject's identity
Pathology studied, date of diagnosis
Medical history, associated diseases (date of onset)
Dates of administration of the study product
Previous and concomitant medications
A statement that the Informed Consent Form was signed by the subject
Dates of participation in the study
Dates of study visits
Assessments performed during the study (including questionnaires)
AEs and SAEs (and follow-up)
Date of dropout (and reason)