Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

A Randomized, Double-Blind, Placebo-Controlled Study of Gelesis100: A Novel Nonsystemic Oral Hydrogel for Weight Loss

Frank L. Greenway[1], Louis J. Aronne[2], Anne Raben[3], Arne Astrup[3], Caroline M. Apovian[4], James O. Hill[5], Lee M. Kaplan[6], Ken Fujioka[7], Erika Matejkova[8], Stepan Svacina[9], Livio Luzi[10], Lucio Gnessi[11], Santiago Navas-Carretero[12], J. Alfredo Martinez[12,13], Christopher D. Still[14], Alessandro Sannino[15], Cosimo Saponaro[15], Christian Demitri[15], Lorien E. Urban[15], Harry Leider[15], Elaine Chiquette[15], Eyal S. Ron[15], Yishai Zohar[15], and Hassan M. Heshmati[15]

Objective: This study aims to assess the efficacy and safety of Gelesis100, a novel, nonsystemic, superabsorbent hydrogel to treat overweight or obesity.

Methods: The Gelesis Loss Of Weight (GLOW) study was a 24-week, multicenter, randomized, double-blind, placebo-controlled study in patients with BMI ≥ 27 and ≤ 40 kg/m^2 and fasting plasma glucose ≥ 90 and ≤ 145 mg/dL. The co-primary end points were placebo-adjusted weight loss (superiority and 3% margin super-superiority) and at least 35% of patients in the Gelesis100 group achieving ≥ 5% weight loss.

Results: Gelesis100 treatment caused greater weight loss over placebo (6.4% vs. 4.4%, P = 0.0007), achieving 2.1% superiority but not 3% super-superiority. Importantly, 59% of Gelesis100-treated patients achieved weight loss of ≥ 5%, and 27% achieved ≥ 10% versus 42% and 15% in the placebo group, respectively. Gelesis100-treated patients had twice the odds of achieving ≥ 5% and ≥ 10% weight loss versus placebo (adjusted OR: 2.0, P = 0.0008; OR: 2.1, P = 0.0107, respectively), with 5% responders having a mean weight loss of 10.2%. Patients with prediabetes or drug-naive type 2 diabetes had six times the odds of achieving ≥ 10% weight loss. Gelesis100 treatment had no apparent increased safety risks.

Conclusions: Gelesis100 is a promising new nonsystemic therapy for overweight and obesity with a highly desirable safety and tolerability profile.

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[1] Pennington Biomedical Research Center of the Louisiana State University System, Baton Rouge, Louisiana, USA [2] Weill Cornell Medicine Comprehensive Weight Control Center, New York, New York, USA [3] Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Frederiksberg C, Denmark [4] Department of Medicine, Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, Massachusetts, USA [5] Department of Pediatrics and Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA [6] Obesity, Metabolism, and Nutrition Institute and Gastrointestinal Unit, Massachusetts General Hospital, Boston, Massachusetts, USA [7] Scripps Clinic Del Mar, San Diego, California, USA [8] Health & Care, sro., Prague, Czech Republic [9] Third Internal Clinic, Charles University, Prague, Czech Republic [10] Department of Endocrinology and Metabolism, Policlinico San Donato, University of Milan, Milan, Italy [11] Experimental Medicine Department, Sapienza University of Rome, Rome, Italy [12] Center for Nutrition Research, University of Navarra, Pamplona, Spain [13] CIBERobn and IMDEA Food Institute, Madrid, Spain [14] Center for Nutrition and Weight, Geisinger Obesity Institute, Danville, Pennsylvania, USA [15] Gelesis, Inc., Boston, Massachusetts, USA. Correspondence: Hassan M. Heshmati (hheshmati@gelesis.com)

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Introduction

Obesity increases the risk for several life-threatening diseases (1-5). Importantly, the increased risk of death is not limited to severe or Class II (BMI 35 to 40 kg/m^2) and Class III (BMI > 40 kg/m^2) obesity but begins in patients who have a BMI of 25 kg/m^2 (6,7) and continues in Class I obesity (BMI 30 to 35 kg/m^2) (8). In fact, 40% of BMI-related deaths and 37% of disability-adjusted life years in 2015 occurred in patients with overweight (4), and Class I obesity was associated with reduced life expectancy by 2 to 4 years (8).

Only 2% of patients with overweight or obesity receive antiobesity drug therapy despite the overwhelming evidence of the growing burden of excess weight (7,9). In contrast, more than 80% of patients with type 2 diabetes (T2D) are prescribed antidiabetes pharmacotherapy (10). Considering that obesity is a major cause of T2D, these realities are paradoxical. Multiple studies documented that therapeutic inertia is high in the management of weight, particularly in patients with lower BMI (11). The highest rates of weight management interventions by primary care physicians occur for patients in the Class III obesity category and the lowest for patients in the overweight category; rates also correlated with the presence of comorbidities (12,13). A 2016 obesity survey among health care professionals reported that 60% of antiobesity pharmacotherapy is disproportionally prescribed for patients in Class II or Class III obesity (11). Health care providers addressing weight management issues are challenged by numerous barriers, but the concerns about tolerability and safety of currently available interventions likely contribute to this resistance to treat obesity (14).

There is thus an urgent need for therapies that increase patients' odds for achieving clinically meaningful weight loss with little or no additional safety risk compared with lifestyle interventions. Such therapies could allow clinicians to intervene earlier in the overweight and obesity continuum and prevent progression or delay associated comorbidities while helping to overcoming the current therapeutic inertia.

Gelesis100 is a nonsystemic, superabsorbent hydrogel developed for the treatment of overweight or obesity. It is made from two naturally derived building blocks, modified cellulose cross-linked with citric acid, that create a three-dimensional matrix. Orally administered in capsules with water before a meal, Gelesis100 particles rapidly absorb water in the stomach and homogeneously mix with ingested foods. When hydrated, the recommended dose of Gelesis100 occupies about one-fourth of the average stomach volume. Rather than forming one large mass, it creates thousands of small individual gel pieces with the elasticity (firmness) of solid ingested foods (e.g., vegetables) without caloric value (15). Gelesis100 maintains its three-dimensional structure and mechanical properties during transit through the small intestine. Once it arrives in the large intestine, the hydrogel is partially broken down by enzymes and loses its three-dimensional structure along with most of its absorption capacity. The released water is reabsorbed, and the remaining cellulosic material is expelled in the feces. Gelesis100 is considered a medical device because it achieves its primary intended purpose through mechanical modes of action (16) consistent with mechanobiology constructs (17). Gelesis100 received a Nonsignificant Risk designation by the Food and Drug Administration.

Herein, we report results from the Gelesis Loss Of Weight (GLOW) pivotal study that assessed the safety and efficacy of Gelesis100 in patients with overweight or obesity, with and without T2D. Results of GLOW's 24-week extension (GLOW-EX) study are also presented.

Methods

Study design and treatment

GLOW was a multicenter, randomized, double-blind, placebo-controlled, pivotal study assessing the safety and efficacy of Gelesis100 administered for 24 weeks on body weight in adults with overweight or obesity, with or without T2D. The 24-week open-label extension study (GLOW-EX) was offered to the last 52 patients who completed treatment (placebo or Gelesis100) and lost ≥ 3% of their body weight from baseline. GLOW and GLOW-EX were conducted in accordance with the Good Clinical Practice guidelines as defined by the International Conference on Harmonisation, the Declaration of Helsinki, the International Organization for Standardization 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects), and all applicable federal and local medical device guidelines and regulations. Institutional review boards, independent ethics committees, and European Competent Authorities approved the study protocol and informed consent documents. A study design schematic of GLOW and GLOW-EX can be found in Supporting Information Figure S1.

For 168 days, patients self-administered three capsules containing either 2.25 g of Gelesis100 or placebo with 500 mL of water 20 to 30 minutes before lunch and dinner. Patients were prescribed a hypocaloric diet of 300 kcal/d below their calculated energy requirement (with 45% to 50% of daily calorie intake from carbohydrates, ≤ 30% from fat, and 20% to 25% from protein). Patients were instructed to perform daily moderate-intensity exercise (e.g., 30 minutes of walking/day) and maintain their smoking habits during the study.

Patients

Eligible patients were men and nonpregnant, nonlactating women aged 22 to 65 years with BMI ≥ 27 and ≤ 40 and fasting plasma glucose (FPG) ≥ 90 and ≤ 145 mg/dL at screening (visit 1). Patients with BMI < 30 were required to have at least one of the following comorbidities: dyslipidemia (defined as serum low-density lipoprotein cholesterol [LDL-C] ≥ 130 and < 190 mg/dL and/or triglycerides [TG] ≥ 150 and < 500 mg/dL), hypertension (supine systolic blood pressure [SBP] ≥ 140 and < 160 mmHg and/or supine diastolic blood pressure [DBP] ≥ 90 and < 95 mmHg), or drug-naive or metformin-treated T2D.

Patients were excluded from the study if they were of childbearing potential and not using contraception; had type 1 diabetes; or had a history of eating disorders (except for mild binge eating disorder), significant gastrointestinal disorders, and gastric bypass or other gastrointestinal surgery. Patients with hemoglobin A_{1c} > 8.5% (> 69 mmol/mol), who had a weight change > 3 kg within 3 months of screening, or who required medications administered with meals were also excluded. Depression was not an exclusion criterion unless it required a drug causing weight change.

Efficacy assessments

GLOW study. The co-primary efficacy end points were the percent change in body weight from baseline (visit 2) to day 171 (visit 13) and the percent of patients who lost ≥ 5% body weight from baseline to day 171. Secondary efficacy end points included percent change in body weight in patients with impaired FPG (IFG) at baseline, change in plasma glucose status in IFG, percent change in plasma glucose in IFG and T2D, change in BMI, and change in hemoglobin A_{1c} in T2D from baseline to day 171. Selected tertiary efficacy end points included

the percent of patients who lost ≥ 10% body weight and percent change from baseline to day 171 in estimated excess body weight, serum insulin, homeostasis model assessment-insulin resistance (HOMA-IR), LDL-C, HDL-C, TG, waist circumference, and supine and standing SBP and DBP. Baseline measurements were assessed on day 0. Treatment began on day 1 and ended on day 169. There were approximately 2 days between the end of treatment and study end point assessments (day 171) to allow the remaining Gelesis100 to be eliminated from the gastrointestinal tract.

GLOW-EX study. The GLOW-EX study evaluated the durability of the efficacy of Gelesis100 over a 48-week exposure and assessed the incremental weight loss benefit by adding Gelesis100 after patients' successful weight loss with lifestyle modification (placebo) over the initial 24 weeks. The co-primary efficacy end points included the percent change in body weight from GLOW baseline (day 0) to day 339 and from GLOW-EX baseline (day 171) to day 339 as well as the percent of patients who lost ≥ 5% body weight from GLOW baseline to day 339 and from GLOW-EX baseline to day 339.

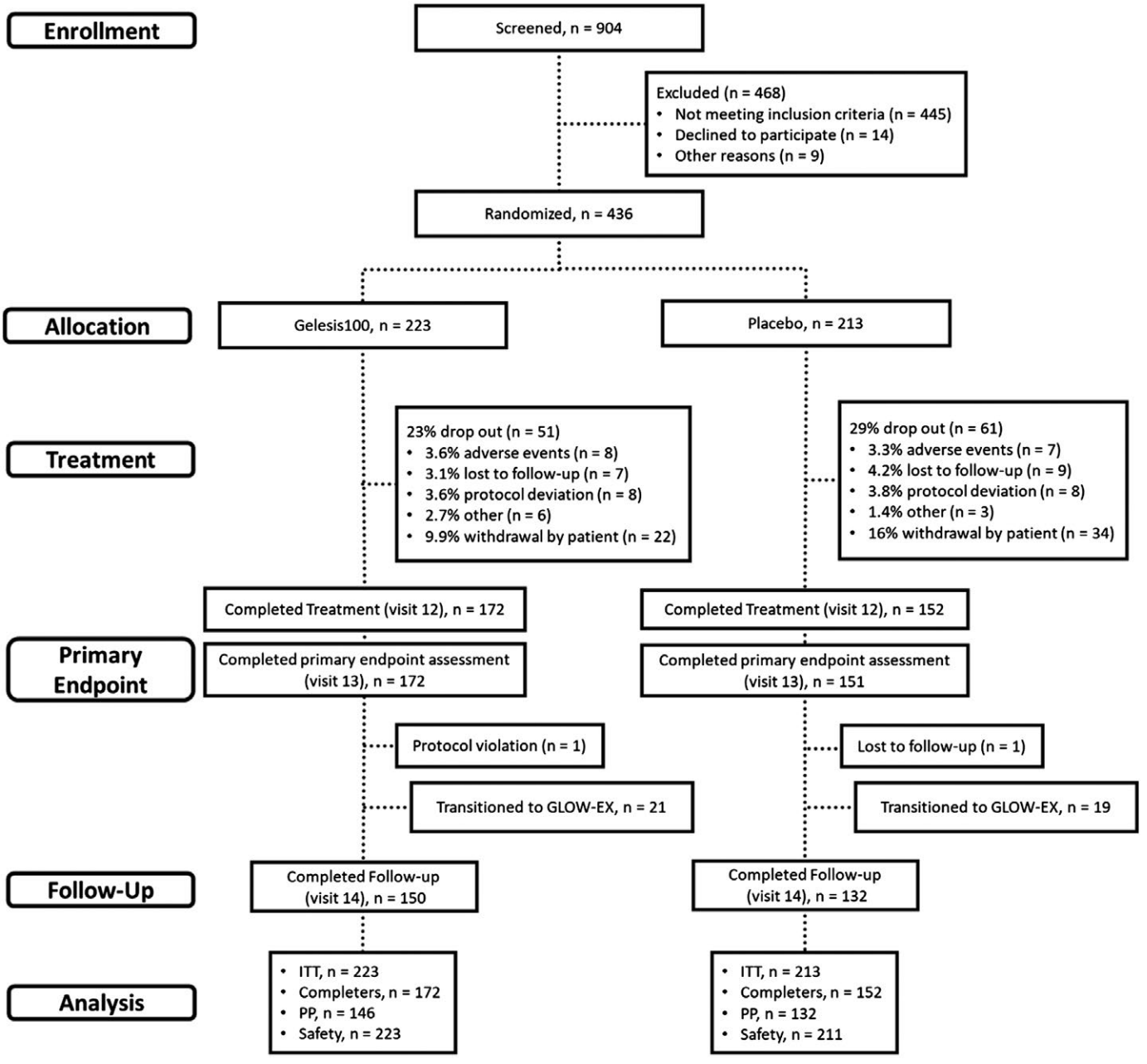

Figure 1 Patient disposition. GLOW, Gelesis Loss Of Weight study; EX, extension; ITT, intention-to-treat; PP, per-protocol.

TABLE 1 Baseline demographics and disease characteristics (ITT population)

Parameter[a]	Gelesis100 (*n* = 223)	Placebo (*n* = 213)	*P* value
Age (y)	48.2 (9.9)	47.8 (10.9)	0.734
			1.0000
Sex, *n* (%)			
Female	125 (56.1)	120 (56.3)	
Male	98 (43.9)	93 (43.7)	
Race, *n* (%)			0.7345
White	189 (84.8)	180 (84.5)	
Black/African American	26 (11.7)	24 (11.3)	
Other	8 (3.5)	9 (4.2)	
Ethnicity, *n* (%)			0.3217
Hispanic or Latino	11 (4.9)	16 (7.5)	
Weight, kg^2	97.6 (14.4)	100.6 (15.3)	0.0348
BMI, kg/m^2	33.5 (3.2)	34.1 (3.2)	0.0784
Waist circumference, cm[b]	108.3 (10.7)	110.7 (11.0)	0.0249
Weight categories, *n* (%)			0.1457
Overweight	26 (11.7)	21 (9.9)	
Obesity Class I	129 (57.8)	108 (50.7)	
Obesity Class II	68 (30.5)	84 (39.4)	
Comorbidities, *n* (%)			0.7557
Dyslipidemia[c]	154 (69.1)	154 (72.3)	0.4406
Hypertension[d]	67 (30.0)	60 (28.2)	0.4638
Prediabetes[e]	66 (29.6)	66 (31.0)	0.6748
T2D	21 (9.4)	25 (11.7)	0.3405
FPG, mg/dL			
Normoglycemia	91.7 (5.7)	91.8 (5.6)	0.8986
Prediabetes	107.7 (5.7)	108.4 (6.5)	0.5414
Drug-naive T2D	133.7 (42.2)	138.2 (8.8)	0.4800
Treated T2D (metformin)	116.2 (19.9)	117.4 (20.3)	0.8690
Insulin, mU/L			
Normoglycemia	9.4 (4.9)	10.1 (5.4)	0.2904
Prediabetes	13.7 (7.3)	12.6 (7.9)	0.4110
Drug-naive T2D	42.2 (58.0)	26.2 (15.7)	0.5047
Treated T2D (metformin)	17.2 (21.7)	13.3 (9.1)	0.5408
HOMA-IR			
Normoglycemia	2.1 (1.1)	2.3 (1.2)	0.3493
Prediabetes	3.7 (2.0)	3.4 (2.1)	0.3999
Drug-naive T2D	15.5 (23.8)	8.8 (5.0)	0.4891
Treated T2D (metformin)	5.6 (8.6)	4.1 (3.4)	0.5426
Current smokers, *n* (%)	23 (10.3)	24 (11.3)	0.7599
Postmenopausal, *n* (%)	57/125 (45.6)	51/120 (42.5)	0.6996
Untreated	55 (96.5)	50 (98.0)	1.0000
Treated (estrogen)	2 (3.5)	1 (2.0)	

[a]Data presented as mean (SD) unless otherwise specified.
[b]Weight and waist circumference parameters significantly different between groups at baseline ($P = 0.0348$ and 0.0249, respectively).
[c]Dyslipidemia defined as serum low-density lipoprotein cholesterol ≥ 130 and <190 mg/dL and/or triglycerides ≥ 150 and <500 mg/dL.
[d]Hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.
[e]Prediabetes was defined based on 1 FPG measurement at visit 2.
FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; T2D, type 2 diabetes; ITT, intention-to-treat.

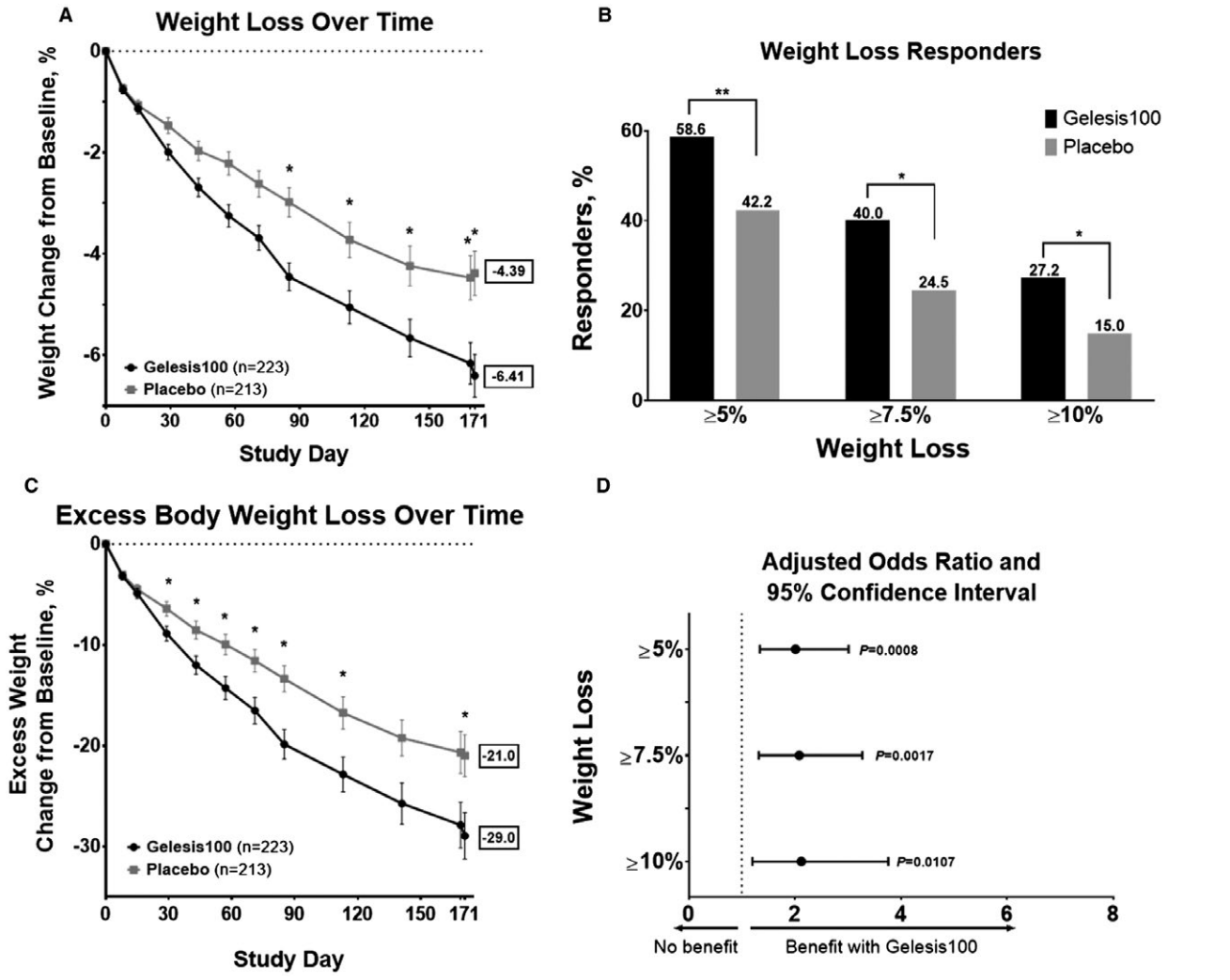

Figure 2 Weight loss with Gelesis100 versus placebo treatment during the GLOW study among patients in the ITT population. (**A**) Percent change in body weight from baseline (day 0) to day 171 (after 2 days of washout) by treatment group. Error bars represent standard error of the mean (SEM). (**B**) Percent responders with ≥ 5% (P = 0.0008), ≥ 7.5% (P = 0.0017), or ≥ 10% (P = 0.0107) weight loss in all patients. (**C**) Percent change in excess body weight from baseline (day 0) to day 171 (after 2 days of washout) by treatment group. Error bars represent SEM. (**D**) Adjusted odds ratio (95% confidence interval) for achieving ≥ 5% (2.0 [1.3-3.0]), ≥ 7.5% (2.1 [1.3-3.3]), and ≥ 10% (2.1 [1.2-3.8]) weight loss. *P< 0.05; **P< 0.001. All P values are from logistic regression models adjusted for baseline weight and stratification factors. GLOW, Gelesis Loss Of Weight study; ITT, intention-to-treat.

Safety assessments

The safety and tolerability of Gelesis100 were assessed by recording all adverse events (AEs) and serious AEs (SAEs) and monitoring results from physical examinations, vital sign measurements, and fasting clinical laboratory tests, which included hematology, blood chemistry, and vitamin levels. For the GLOW study, all AEs and SAEs reported after randomization and up to 28 days after the last treatment administration (day 197) were recorded. For the GLOW-EX study, all AEs and SAEs reported up to 28 days after the last treatment administration (day 365) were recorded.

Statistical analysis

Sample size was calculated using PASS power analysis software (NCSS, LLC, Kaysville, Utah). A total of 430 patients were randomized 1:1 to have 172 completers per treatment group based on 20% dropout rate. This sample size was expected to provide 85% statistical power to detect a difference of ≥ 3% weight loss and 90% statistical power to establish that the difference between the two treatment groups was greater than 0 (superiority with a standard deviation [SD] of 5.0% and a type I error of 0.05 in a two-sided test). The co-primary end points were placebo-adjusted percent weight loss super-superiority with a margin of 3% and at least 35% of patients on Gelesis100 achieving at least 5% weight loss. A prespecified analysis of simple superiority was also performed. Stratification factors using characteristics obtained at the screening visit were used to balance treatment group assignments. The stratification was based on groups of countries, sex, BMI, and screening FPG at the time of randomization.

In the pilot clinical study First Loss Of Weight (FLOW), elevated FPG and particularly prediabetes status at baseline were associated with greater weight loss in patients treated with Gelesis100 (18). To evaluate this hypothesis further, GLOW included screening FPG as a stratification factor.

Continuous variables are presented as mean (SD) unless otherwise specified. Statistical software SAS version 9.3 or later (SAS Institute, Inc., Cary, North Carolina) was used for statistical analysis. The primary efficacy analysis was performed using the intention-to-treat (ITT) population consisting of all randomized patients, with missing data imputed using a robust multiple imputation analysis (SAS PROC MI, SAS Institute). For the two treatment groups, analysis of covariance (ANCOVA) was performed to compare the percent change in body weight from baseline to day 171 (two-sided $\alpha = 0.05$). The logit model was used to determine the percent body weight responders. Secondary and tertiary end points were analyzed using a closed test procedure with ANCOVA. All *P* values are from logistic regression models adjusted for baseline weight and stratification factors. HOMA-IR was calculated by multiplying fasting serum insulin (mU/L) by FPG (mmol/L) and dividing by 22.5.

Additional analyses included weight loss-related end points among FPG subgroups (based on two consecutive FPG measurements per American Diabetes Association guidelines) (19) who had no missing data (completers). An area under the curve (AUC) of the receiver operating characteristic (ROC) was completed as a post hoc analysis to model the predictive power of early weight loss for responder status with the optimal point determined by the Youden index. The AUC ROC analysis optimized the balance between positive predictive value or percent of patients with early weight loss response who had ≥ 5% weight loss after 24 weeks and negative predictive value or the percent of patients with early weight loss response who had < 5% weight loss after 24 weeks. The cutoff for positive predictive value and negative predictive value was set at 80%.

The safety population was defined as any patient receiving at least one dose of investigational product after randomization. Safety data are reported as number of patients experiencing an event, using a 95% confidence interval (CI) for AE comparison across treatment groups. The 95% CI was calculated using the Clopper-Pearson method.

GLOW-EX effectiveness end points were assessed by comparing the 95% CI from baseline of GLOW to day 171, and from baseline of

TABLE 2 Change from baseline for weight-related and comorbidity parameters.

	Mean change (SD)[a]		LS mean difference (SD)	95% CI	*P* value
Parameter[b]	**Gelesis100 (*n* = 223)**	**Placebo (*n* = 213)**			
Weight-related					
Weight, %	−6.4 (5.8)	−4.4 (5.5)	−2.1 (0.6)	(−3.2, −0.9)	0.0007
Body mass index, kg/m^2	−2.1 (1.9)	−1.5 (1.9)	−0.6 (0.2)	(−1.0, −0.2)	0.0039
Excess body weight, %	−29.0 (30.1)	−21.0 (25.7)	−6.4 (2.9)	(−12.2, −0.6)	0.0295
Waist circumference, cm	−6.7 (5.6)	−5.0 (5.9)	−1.9 (0.6)	(−3.1, −0.6)	0.0038

	Mean change (95% CI)[e]				
Parameter[b]	**Gelesis100 (*n* = 223)**	**Placebo (*n* = 213)**	**Difference (SD)**	**95% CI**	***P* value**
Comorbidity					
Dyslipidemia[c]					
LDL-C, %	n = 83	n = 84			0.0347
	−11.2 (−14.5, −7.8)	−5.9 (−8.8, −3.0)	−4.7 (2.2)	(−9.0, −0.3)	
TG, %	n = 58	n = 53			0.2694
	−18.0 (−30.0, −5.9)	−8.0 (−23.3, 7.4)	−11.0 (9.9)	(−30.7, 8.7)	
Hypertension[d]					
	n = 38	n = 34		(−5.7, 3.6)	0.6528
SBP, mmHg	−9.3 (−12.4, −6.2)	−9.2 (−12.8, −5.6)	−1.0 (2.3)		
DBP, mmHg	−7.5 (−9.6, −5.4)	−4.7 (−7.2, −2.2)	−1.3 (1.4)	(−4.1, 1.4)	0.3452
Conversion to normotensive, %[f]	68.4	44.1	OR 2.9	(1.0, 7.9)	0.0434

[a]Data presented as mean change (SD) unless otherwise specified.
[b]Parameters are percent change unless otherwise specified.
[c]Dyslipidemia defined as LDL-C >130 mg/dL or TG >150 mg/dL at baseline (LDL-C/TG baseline values = 161/227 mg/dL for Gelesis100 and 159/222 mg/dL for placebo).
[d]Hypertension is defined as SBP >140 mmHg or DBP >90 mmHg at baseline (SBP/DBP baseline values = 143.5/88.5 mmHg and 145.0/85.9 mmHg for Gelesis100 and placebo, respectively).
[e]Completer data presented as mean (95% CI).
[f]OR and 95% CI from logistic regression model adjusted for stratification factors and baseline SBP and DBP.
LS, least squares; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure.

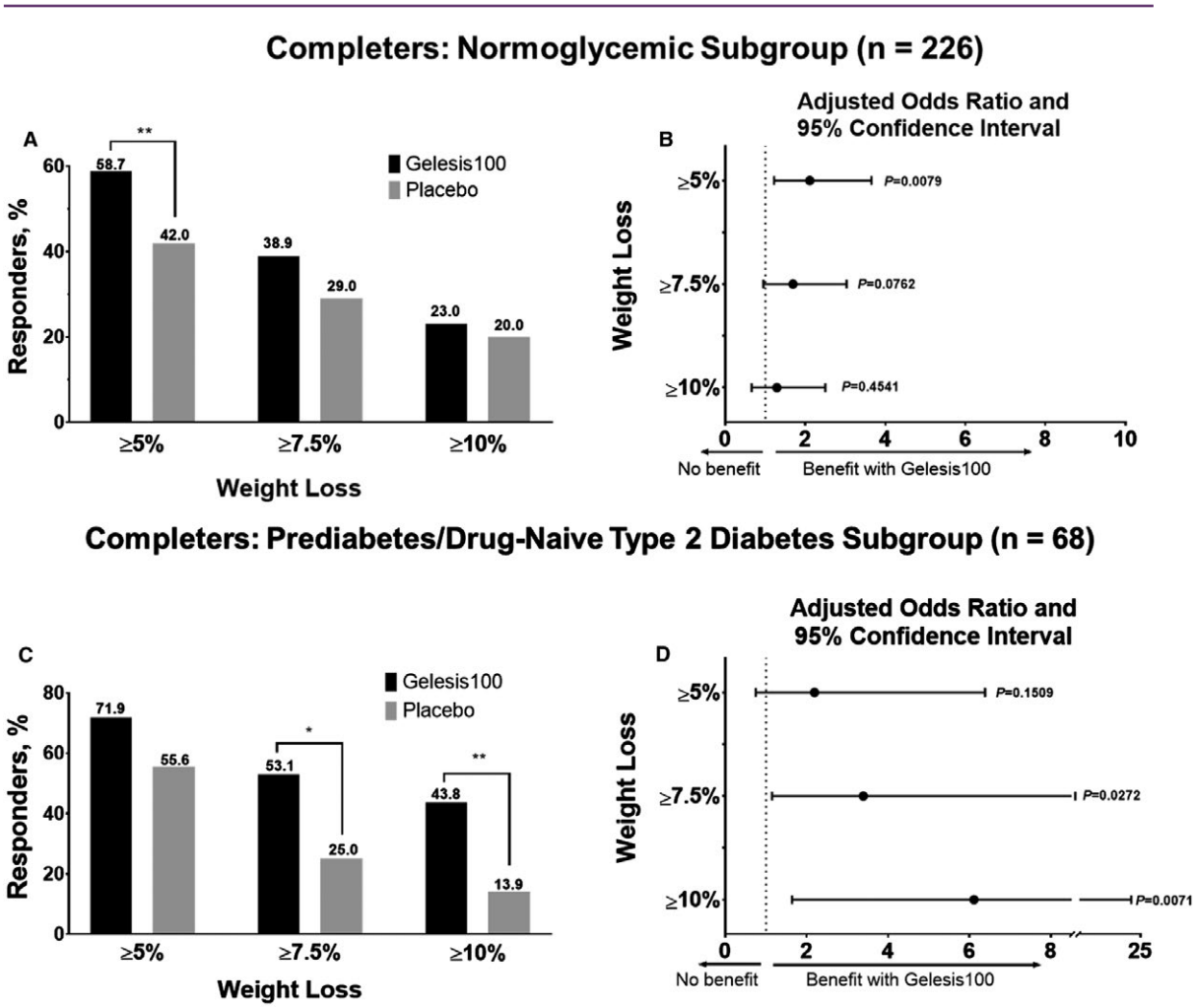

Figure 3 Weight loss with Gelesis100 versus placebo treatment during the GLOW study among completers. (**A**) Percent responders with ≥ 5% (Gelesis100, *n* = 74; placebo, *n* = 42; *P* = 0.0079), ≥ 7.5% (Gelesis100, *n* = 49; placebo, *n* = 49; *P* = 0.0726), and ≥ 10% (Gelesis100, *n* = 29; placebo, *n* = 20; *P* = 0.4541) weight loss in normoglycemic completers (*n* = 226). (**B**) Adjusted odds ratio (95% confidence interval) of ≥ 5% (2.1 [1.2-3.7]), ≥ 7.5% (1.7 [1.0-3.0]), and ≥ 10% (1.3 [0.7-2.5]) weight loss achieved by normoglycemic completers between treatment groups. (**C**) Percent responders with ≥ 5% (Gelesis100, *n* = 23; placebo, *n* = 20; *P* = 0.1509), ≥ 7.5% (Gelesis100, *n* = 17; placebo, *n* = 9; *P* = 0.0272), and ≥ 10% (Gelesis100, *n* = 14; placebo, *n* = 5; *P* = 0.0071) weight loss in completers with prediabetes or drug-naive T2D (*n* = 68). (**D**) Adjusted odds ratio (95% confidence interval) of ≥ 5% (2.2 [0.8-6.4]), ≥ 7.5% (3.4 [1.2-10.0]), and ≥ 10% (6.1 [1.6-22.8]) weight loss achieved by completers with prediabetes or drug-naive T2D between treatment groups. T2D, type 2 diabetes. *$P < 0.05$; **$P < 0.01$. All *P* values are from logistic regression models adjusted for baseline weight and stratification factors. GLOW, Gelesis Loss Of Weight study.

GLOW to day 339, with the overlapping 95% CI representing maintenance of the effect. Percent change in body weight from baseline of GLOW or GLOW-EX to day 339 and *P* values were determined using paired *t* tests (two-sided $\alpha = 0.05$) for both treatment groups.

Results

Patient disposition and baseline demographics

Of the 904 patients screened for eligibility, 436 were randomized (223 patients allocated to the Gelesis100 group and 213 patients allocated to the placebo group), and 324 completed the treatment phase of the GLOW study (172 in the Gelesis100 group and 152 in the placebo group) (Figure 1). A total of 112 patients were withdrawn from the study (51 [23%] in the Gelesis100 group and 61 [29%] in the placebo group). The most common reason for withdrawal by patient was for lifestyle or personal choice (Figure 1).

Demographics and baseline characteristics were overall similar between groups (Table 1). Patients were mostly middle-aged, white, and equally distributed across the treatment groups by sex. A total of 284 patients (70% of the Gelesis100 group and 61% of the placebo group) had either overweight or Class I obesity. Baseline weight

TABLE 3 AUC ROC analysis for 5% responders in Gelesis100 and placebo groups.

Percent change in weight from baseline	Optimal threshold	Sensitivity	Specificity	AUC	SE[a]	Lower 95% CI[b]	Upper 95% CI[b]
Gelesis100							
Visit 3, week 1	−0.9106	0.5657	0.7324	0.6795	0.0423	0.5966	0.7625
Visit 4, week 2	−1.3793	0.6000	0.7917	0.7727	0.0352	0.7037	0.8417
Visit 5, week 4	−2.2876	0.7400	0.8310	0.8515	0.0285	0.7956	0.9075
Visit 6, week 6	−2.8678	0.7600	0.8310	0.8811	0.0247	0.8326	0.9296
Visit 7, week 8	**−3.0272**	**0.8485**	**0.8732**	**0.9105**	**0.0216**	**0.8683**	**0.9528**
Visit 8, week 10	−3.1504	0.8485	0.8592	0.9175	0.0206	0.8772	0.9578
Visit 9, week 12	−3.4913	0.9000	0.8333	0.9242	0.0195	0.8859	0.9624
Visit 10, week 16	−4.2219	0.9100	0.8889	0.9590	0.0128	0.9339	0.9840
Visit 11, week 20	−4.1945	0.9600	0.8889	0.9818	0.0070	0.9681	0.9955
Visit 12, week 24	−5.1163	0.9500	1.0000	0.9965	0.0021	0.9924	1.0000
Placebo							
Visit 3, week 1	−1.4541	0.4531	0.8636	0.6779	0.0443	0.5911	0.7647
Visit 4, week 2	−2.1179	0.5238	0.8636	0.7335	0.0416	0.6519	0.8151
Visit 5, week 4	−1.7578	0.7813	0.7614	0.8215	0.0348	0.7534	0.8897
Visit 6, week 6	−3.2967	0.6563	0.8864	0.8267	0.0348	0.7586	0.8948
Visit 7, week 8	−2.1951	0.8438	0.7614	0.8823	0.0269	0.8295	0.9350
Visit 8, week 10	−4.0948	0.6825	0.9318	0.8864	0.0257	0.8359	0.9368
Visit 9, week 12	−4.0000	0.7813	0.8864	0.9119	0.0219	0.8690	0.9549
Visit 10, week 16	**−4.8048**	**0.8438**	**0.9342**	**0.9414**	**0.0185**	**0.9051**	**0.9777**
Visit 11, week 20	−4.8908	0.9063	0.9342	0.9729	0.0113	0.9508	0.9951
Visit 12, week 24	−4.7668	0.9688	0.9773	0.9952	0.0030	0.9893	1.0011

The first time point in which sensitivity and specificity were both above 80% occurred at week 8 for Gelesis100 and week 16 for placebo (represented in bold).
Optimal threshold to predict 5% or greater weight loss at 24 weeks in Gelesis100 group is at least 3% weight loss at 8 weeks. Early responders achieved mean weight loss of 9.9% at week 24 versus 2.1% for non-early responders.
When applying the threshold of 3% weight loss at 8 weeks to placebo group, mean weight loss of 8.9% at week 24 for early responders versus 1.5% for non-early responders was observed. However, the analysis for placebo group demonstrated predictive values >0.8 only at 16 weeks with weight loss threshold of 4.8%.
AUC, area under the curve; ROC, receiver operating characteristic.
[a]SE of AUC.
[b]95% CI for AUC.

and waist circumference were significantly lower in the Gelesis100 group versus placebo (P = 0.0348 and P = 0.0249, respectively). The primary end point analyses account for this difference, as baseline BMI and weight were covariates in the ANCOVA models. At baseline, most patients had high normal FPG ≥ 90 mg/dL (136/223 patients [61%] in the Gelesis100 group and 122/213 patients [57%] in the placebo group).

GLOW results

Efficacy. In the ITT population, there was a greater percent change in body weight from baseline to day 171 in the Gelesis100 group (mean −6.4% [SD 5.8%]) versus placebo (mean −4.4% [SD 5.5%]) (Figure 2A), with a placebo-adjusted least squares mean difference of −2.1% (P = 0.0007) (Table 2). The study demonstrated superiority over placebo but not super-superiority with 3% margin.

Notably, significantly more patients treated with Gelesis100 achieved ≥ 5% weight loss (co-primary end point) versus placebo (59% vs. 42%) (Figure 2B), and 27% of patients treated with Gelesis100 achieved ≥ 10% weight loss versus 15% of patients treated with placebo. Patients treated with Gelesis100 had twice the odds of achieving ≥ 5% weight loss versus placebo (adjusted odds ratio [OR]: 2.0; P = 0.0008). For these responders, the mean weight loss was 10.2% ± 4.1%. Similarly, Gelesis100-treated patients had twice the odds of achieving ≥ 7.5% (OR: 2.1; P = 0.0017) and ≥ 10% (OR: 2.1; P = 0.0107) weight loss (Figure 2D). Patients treated with Gelesis100 sustained markedly greater weight loss over time without plateauing (Figure 2A).

Of the secondary end points, only reduction in BMI reached statistical significance versus placebo (P = 0.0039). In addition to the percent of patients achieving ≥ 10% weight loss, the other tertiary end points that were statistically different were excess body weight (Figure 2C; P = 0.0295) and waist circumference (P = 0.0038) (Table 2).

Predictors of response. In a previous clinical study (FLOW), an association was observed between elevated FPG and greater treatment effect, particularly among patients with FPG ≥ 100 mg/dL at baseline 18. In the GLOW study, there were 32 patients in the Gelesis100 group

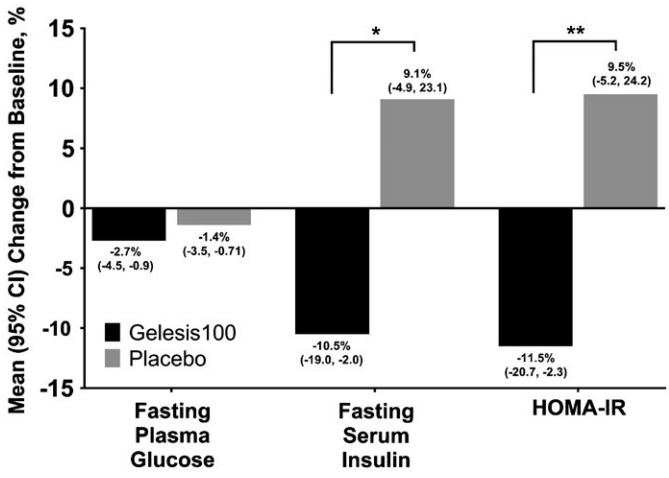

Figure 4 Percent change from baseline in glycemic control parameters (completers with baseline FPG ≥ 90 mg/dL and not treated with antidiabetes medication). Baseline FPG was 100.9 mg/dL in the Gelesis100 group and 102.5 mg/dL in the placebo group. Mean percent change (95% CI) from baseline in FPG in Gelesis100 (n = 121) and placebo (n = 111; P = 0.1872). Baseline fasting serum insulin was 11.5 mU/L in the Gelesis100 group and 12.1 mU/L in the placebo group. Mean percent change (95% CI) from baseline in fasting serum insulin in Gelesis100 (n = 120) and placebo (n = 111; P = 0.0102). Baseline HOMA-IR was 2.9 in the Gelesis100 group and 3.2 in the placebo group. Mean percent change (95% CI) from baseline in HOMA-IR in Gelesis100 (n = 120) and placebo (n = 111; P = 0.0080). *P < 0.05; **P < 0.01.FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance.

and 36 patients in the placebo group with prediabetes (FPG ≥ 100 mg/dL and < 126 mg/dL) or drug-naive T2D (FPG ≥ 126 mg/dL), based on two consecutive FPG measurements at visit 1 and visit 2. The mean (SD) percent change in body weight from baseline to day 171 was −8.1% (6.5%) and −5.6% (4.9%) for the Gelesis100 and placebo treatment groups, respectively (adjusted mean standard error [SE] difference of −2.5% [1.4]; P = 0.0820).

More patients with prediabetes or drug-naive T2D (53%) achieved ≥ 7.5%, and almost half (44%) achieved ≥ 10% weight loss versus 25% and 14% of patients in the placebo group, respectively (Figure 3C). The odds of achieving ≥ 7.5% or ≥ 10% weight loss were 3.4 and 6.1 times higher in the Gelesis100 group versus the placebo group (P = 0.0272 and 0.0071, respectively) (Figure 3D).

AUC ROC analysis showed that early response to Gelesis100 treatment (≥ 3% weight loss from baseline at week 8) successfully predicted clinically meaningful weight loss (≥ 5%) at 24 weeks. More than 85% of patients who went on to achieve ≥ 5% weight loss at 6 months had lost ≥ 3% of body weight at 8 weeks. Notably, early responders achieved mean weight loss of 9.9% versus 2.1% in nonearly responders at week 24 (Table 3). The placebo group did not reach the required threshold for sensitivity and specificity until near the end of treatment (Table 3).

Effect on cardiovascular risk factors. Overall, there were no significant differences between groups in the well-known cardiovascular risk factors such as LDL-C, HDL-C, TG, SBP, DBP, or insulin resistance estimated by HOMA-IR. However, in patients who started with elevated levels, those treated with Gelesis100 had a greater reduction in LDL-C levels (P = 0.0347) and greater conversion rate to normal blood pressure (P = 0.0434) (Table 2). Patients with elevated HOMA-IR at baseline treated with Gelesis100 had a reduction compared with the placebo group (P = 0.0080) (Figure 4). This improvement in HOMA-IR was mainly driven by a reduction in fasting serum insulin in the Gelesis100 group (P = 0.0102).

Safety. All 436 patients in the GLOW study are included in the safety analysis except for 2 patients in the placebo group who did not receive the investigational product. The most common AEs in both groups were gastrointestinal related, infections and infestations, and musculoskeletal and connective tissue disorders. The most common (> 5%) gastrointestinal AEs in the Gelesis100 group were diarrhea, abdominal distension, infrequent bowel movements, flatulence, constipation, nausea, and abdominal pain. In the Gelesis100 group, 158 (85%) gastrointestinal AEs reported by 84 (38%) patients were deemed possibly or probably related to the study treatment versus 105 (78%) AEs reported by 58 (28%) patients in the placebo group (P = 0.0248). Fifteen patients withdrew from the study because of an AE (eight in the Gelesis100 group and seven in the placebo group) before completing the treatment phase; five in the Gelesis100 group and four in the placebo group were considered probably or possibly related to the study treatment (Table 4).

Overall, gastrointestinal-related AEs were significantly different between groups (P = 0.0248). However, none of the individual gastrointestinal AEs, regardless of their level of severity, reached statistical significance. Most of these events were assessed as mild. The incidence of gastrointestinal events considered to be either moderate or severe was 39 events in 21 patients in the Gelesis100 group and 22 events in 15 patients in the placebo group.

In the Gelesis100 group, eight patients reported an SAE versus ten patients in the placebo group. The majority of SAEs occurred within 3 months of randomization and were resolved within 2 weeks without sequelae. In the placebo group, one patient (0.5%) reported an SAE of a benign colon tumor. No patients in the Gelesis100 group reported an SAE. No deaths occurred during the study.

There were no significant differences in the serum levels of vitamins A, B1, B2, B6, B9, B12, and D between the two groups in the subcohort whose vitamin levels were measured.

In summary, other than an increase in overall gastrointestinal AEs, there was no difference in the incidence and severity of AEs between the Gelesis100 and placebo groups. In both treatment groups, most AEs were mild or moderate in intensity, occurred within the first 3 months, and resolved within 2 weeks (Table 4).

GLOW-EX results

GLOW-EX was offered to the last 52 completers of the GLOW study (Gelesis100 and placebo groups) who had lost ≥ 3% body weight from baseline. Of these eligible patients, 39 (21 from the Gelesis100 group and 18 from the placebo group) enrolled in GLOW-EX. Patients treated with Gelesis100 in GLOW achieved a mean of 7.1% (SD 2.8%) weight loss at the time of enrollment in GLOW-EX. Continuation of

TABLE 4 Adverse events (safety population).

	Patients, n (%)				Patients, n (%)			
	All				Probably or possibly related			
	Gelesis100 (n = 223)	Placebo (n = 211)	Difference (95% CI)	*P* value	Gelesis100 (n = 223)	Placebo (n = 211)	Difference (95% CI)	*P* value
Summary								
Any AE	159 (71.3)	149 (70.6)	0.7 (–8.1 to 9.5)	0.9159	88 (39.5)	64 (30.3)	9.1 (–0.2 to 18.2)	0.0557
Mild	124 (55.6)	117 (55.5)	0.2 (–9.4 to 9.8)	1.0000	75 (33.6)	54 (25.6)	8.0 (–0.9 to 16.8)	0.0744
Moderate	88 (39.5)	83 (39.3)	0.1 (–9.3 to 9.6)	1.0000	24 (10.8)	18 (8.5)	2.2 (–3.8 to 8.2)	0.5165
Severe	8 (3.6)	10 (4.7)	–1.2 (–5.6 to 3.1)	0.6335	3 (1.3)	2 (0.4)	0.4 (–2.6 to 3.4)	1.0000
Withdrawal due to AE	8 (3.6)	7 (3.3)	0.3 (–3.9 to 4.3)	1.0000	5 (2.2)	4 (1.9)	0.3 (–3.2 to 3.8)	1.0000
System organ class AEs (most common [≥ 2%])								
Blood and lymphatic system disorders	1 (0.4)	1 (0.5)	–0.0 (–2.6 to 2.4)	1.0000	0 (0)	0 (0)		
Cardiac disorders	0 (0)	1 (0.5)	–0.5 (–3.0 to 1.7)	0.4862	0 (0)	0 (0)		
Ear and labyrinth disorders	0 (0)	2 (0.9)	–0.9 (–3.7 to 1.3)	0.2358	0 (0)	0 (0)		
Eye disorders	6 (2.7)	2 (0.9)	1.7 (–1.5 to 5.2)	0.2860	0 (0)	1 (0.5)	–0.5 (–3.0 to 1.7)	0.4862
Gastrointestinal related	96 (43.0)	72 (34.1)	8.9 (–0.6 to 18.2)	0.0614	84 (37.7)	58 (27.5)	10.2 (1.0 to 19.1)	0.0248
Diarrhea	28 (12.6)	18 (8.5)	4.0 (–2.2 to 10.2)	0.2121	23 (10.3)	16 (7.6)	2.7 (–3.1 to 8.5)	0.4015
Abdominal distension	26 (11.7)	14 (6.6)	5.0 (–0.8 to 10.9)	0.0959	24 (10.8)	12 (5.7)	5.1 (–0.5 to 10.7)	0.0579
Infrequent bowel movements	21 (9.4)	10 (4.7)	4.7 (–0.6 to 10.0)	0.0641	20 (9.0)	10 (4.7)	4.2 (–1.0 to 9.5)	0.0910
Flatulence	19 (8.5)	11 (5.2)	3.3 (–1.9 to 8.6)	0.1899	19 (8.5)	10 (4.7)	3.8 (–1.4 to 9.0)	0.1272
Abdominal pain	12 (5.4)	6 (2.8)	2.5 (–1.8 to 6.9)	0.2313	11 (4.9)	6 (2.8)	2.1 (–2.1 to 6.4)	0.3258
Constipation	12 (5.4)	11 (5.2)	0.2 (–4.7 to 4.9)	1.0000	10 (4.5)	10 (4.7)	–0.3 (–4.9 to 4.2)	1.0000
Nausea	11 (4.9)	11 (5.2)	–0.3 (–5.1 to 4.4)	1.0000	8 (3.6)	8 (3.8)	–0.2 (–4.5 to 3.9)	1.0000
Dyspepsia	9 (4.0)	2 (0.9)	3.1 (–0.4 to 6.9)	0.0632	7 (3.1)	2 (0.9)	2.2 (–1.1 to 5.8)	0.1766
Frequent bowel movements	8 (3.6)	7 (3.3)	0.3 (–3.9 to 4.3)	1.0000	8 (3.6)	7 (3.3)	0.3 (–3.9 to 4.3)	1.0000
Abdominal pain upper	0 (0)	9 (4.3)	–2.0 (–6.2 to 1.8)	0.2830	4 (1.8)	5 (2.4)	–0.6 (–4.2 to 2.8)	0.7454
Feces hard	2 (0.9)	5 (2.4)	–1.5 (–4.9 to 1.6)	0.2730	2 (0.9)	5 (2.4)	–1.5 (–4.9 to 1.6)	0.2730
General disorders and administration site conditions	9 (4.0)	16 (7.6)	–3.5 (–8.6 to 1.3)	0.1486	1 (0.4)	1 (0.5)	–0.0 (–2.6 to 2.4)	1.0000
Hepatobiliary disorders	1 (0.4)	0 (0)	0.4 (–1.8 to 2.9)	1.0000	0(0)	0 (0)		
Infections and infestations	74 (33.2)	70 (33.2)	0.0 (–9.1 to 9.1)	1.0000	2 (0.9)	1 (0.5)	0.4 (–2.2 to 3.1)	1.0000
Nasopharyngitis	26 (11.7)	30 (14.2)	–2.6 (–9.3 to 4.1)	0.4750	0 (0)	0 (0)		
Influenza	9 (4.0)	10 (4.7)	–0.7 (–5.3 to 3.7)	0.8162	0 (0)	0 (0)		
Upper respiratory tract infection	8 (3.6)	12 (5.7)	–2.1 (–6.8 to 2.3)	0.3623	0 (0)	0 (0)		
Bronchitis	5 (2.2)	1 (0.5)	1.8 (–1.1 to 5.0)	0.2166	0 (0)	0 (0)		
Gastroenteritis	5 (2.2)	4 (1.9)	0.3 (–3.2 to 3.8)	1.0000	0 (0)	0 (0)		
Viral infection	4 (1.8)	5 (2.4)	–0.6 (–4.2 to 2.8)	0.7454	0 (0)	0 (0)		
Injury, poisoning, and procedural complications	22 (9.9)	12 (5.7)	4.2 (–1.3 to 9.7)	0.1116	0 (0)	0 (0)		
Investigations	10 (4.5)	7 (3.3)	1.2 (–3.1 to 5.4)	0.6244	3 (1.3)	3 (1.4)	–0.1 (–3.3 to 3.0)	1.0000

	Patients, n (%)				Patients, n (%)			
	All				Probably or possibly related			
	Gelesis100 (n = 223)	Placebo (n = 211)	Difference (95% CI)	*P* value	Gelesis100 (n = 223)	Placebo (n = 211)	Difference (95% CI)	*P* value
Back pain	8 (3.6)	10 (4.7)	−1.2 (−5.6 to 3.1)	0.6335	0 (0)	0 (0)		
Arthralgia	7 (3.1)	13 (6.2)	−3.0 (−7.7 to 1.4)	0.1702	0 (0)	0 (0)		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.4)	3 (1.4)	−1.0 (−4.0 to 1.7)	0.3599	0 (0)	0 (0)		
Nervous system disorders	27 (12.1)	22 (10.4)	1.7 (−4.7 to 8.0)	0.6499	4 (1.8)	2 (0.9)	0.8 (−2.2 to 4.0)	0.6860
Headache	16 (7.2)	18 (8.5)	−1.4 (−7.0 to 4.1)	0.7213	2 (0.9)	2 (0.9)	−0.1 (−2.9 to 2.7)	1.0000
Psychiatric disorders	4 (1.8)	3 (1.4)	0.4 (−2.9 to 3.6)	1.0000	0 (0)	0 (0)		
Renal and urinary disorders	3 (1.3)	6 (2.8)	−1.5 (−5.2 to 1.8)	0.3269	1 (0.4)	0 (0)	0.4 (−1.8 to 2.9)	1.0000
Reproductive system and breast disorders	4 (1.8)	4 (1.9)	−0.1 (−3.5 to 3.2)	1.0000	0 (0)	1 (0.5)	−0.5 (−3.0 to 1.7)	0.4862
Respiratory, thoracic, and mediastinal disorders	6 (2.7)	13 (6.2)	−3.5 (−8.1 to 0.8)	0.1002	1 (0.4)	1 (0.5)	−0.0 (−2.6 to 2.4)	1.0000
Oropharyngeal pain	1 (0.4)	6 (2.8)	−2.4 (−6.0 to 0.5)	0.0615	0 (0)	0 (0)		
Skin and subcutaneous tissue disorders	5 (2.2)	5 (2.4)	−0.1 (−3.8 to 3.4)	1.0000	1 (0.4)	3 (1.4)	−1.0 (−4.0 to 1.7)	0.3599
Vascular disorders	3 (1.3)	2 (0.9)	0.4 (−2.6 to 3.4)	1.0000	0 (0)	0 (0)		

AE, adverse event.

Gelesis100 resulted in a mean of 7.6% (SD 5.1%) weight loss at 48 weeks (ITT population, $P < 0.0001$ from GLOW baseline), showing maintenance of weight loss at 48 weeks. Patients treated with placebo in GLOW achieved a mean of 7.1% (SD 4.1%) weight loss at the time of enrollment in GLOW-EX. Addition of Gelesis100 resulted in a mean of 9.4% (SD 6.4%) weight loss at 48 weeks (ITT population, $P < 0.0001$ from GLOW baseline). GLOW-EX safety results were consistent with the GLOW safety data. During GLOW-EX, no SAEs were reported.

Discussion

Results from the GLOW study demonstrate that Gelesis100 is an effective weight loss therapy that is safe and well tolerated. Repeated administration of Gelesis100 over 6 months resulted in significant weight loss over placebo ($P = 0.0007$). Although the placebo-adjusted weight loss was 2.1% and did not reach the 3% threshold, importantly, 59% of patients treated with Gelesis100 lost ≥ 5% of their body weight (co-primary end point) and 27% lost ≥ 10%, versus 42% and 15% with placebo, respectively. The odds to achieve both thresholds were doubled versus placebo (adjusted OR). Of note, Gelesis100 treatment had no increased safety risk, and only gastrointestinal AEs, when combined, were reported at a higher (9%) incidence than with placebo. Notably, only five patients withdrew from the Gelesis100 group because of gastrointestinal-related AEs versus four from the placebo group.

New tools are needed to supplement lifestyle management for treatment of overweight and obesity. There is a particular need for treatments that produce significant weight loss without major AEs (11,14). The outstanding safety profile of Gelesis100 combined with its demonstrated efficacy should make it an attractive option for obesity treatment.

There is wide interindividual variability in response to weight loss therapies, and it would be helpful to understand how to better match treatment to the patient (20). The availability of reliable weight loss predictors would increase the probability of patients achieving and maintaining weight loss and could improve cost-effectiveness (20). The GLOW study revealed the following two useful tools that could support a personalized approach utilizing Gelesis100 and guide clinicians in selecting patients who will benefit the most from treatment: FPG and weight loss achieved as early as 8 weeks of therapy.

In the FLOW pilot study, an unexpected association was observed between baseline FPG levels and the effectiveness of the treatment (18). The GLOW study replicated these findings. Despite the fact that in patients with prediabetes or drug-naive T2D the difference between the treatment groups for achieving ≥ 5% weight loss was not significant, as the thresholds for weight loss became higher and harder to achieve, the difference became substantial and significant. Similarly, the increase in 5% responders over normoglycemic patients was the same in both treatment groups. However, a clear difference favoring Gelesis100 was observed in the 7.5% and 10% responder groups (Figure 3). When taking Gelesis100, the odds of achieving ≥ 10% weight loss were six times higher compared with placebo for patients with prediabetes or drug-naive T2D. This finding demonstrated a benefit for a higher-risk population otherwise known to be less responsive to therapy. Although this population was relatively small ($n = 68$), these findings, in addition to the results of the

FLOW study, suggest that FPG could be a simple predictor that may be used as a tool for identifying patients who are both at higher clinical risk and more likely to achieve greater levels of weight loss when treated with Gelesis100.

Early response to treatment is an additional tool to predict the effectiveness of Gelesis100 treatment with a high level of precision. Results of AUC ROC analysis suggest that a weight loss of ≥ 3% after as few as 8 weeks of treatment with Gelesis100 is predictive of a weight loss of ≥ 5% after 6 months. Notably, early responders achieved a mean weight loss of 9.9% versus 2.1% in nonearly responders at week 24. Although there are no overall increased safety risks with Gelesis100, predicting successful treatment early allows efficient use of resources and provides a key milestone to motivate patients with overweight or obesity.

Long-term weight loss maintenance is difficult to achieve solely with lifestyle modification interventions (21,22). Weight loss was maintained for an additional 24 weeks among the 21 participants who lost at least 3% with Gelesis100 after 6 months in the GLOW study and who were enrolled in the GLOW-EX study.

Considering the repeated intriguing findings in patients with elevated FPG and the observed reduction in insulin resistance in the Gelesis100 group (Figure 4), future studies should confirm these findings and explore the underlying mechanisms of action.

Given the evident safety profile of Gelesis100, it is important to undertake clinical studies in the pediatric population. Also, as the treatment of patients with overweight or obesity often involves multiple strategies, future studies of Gelesis100 treatment in combination with other therapeutic approaches are warranted.

In conclusion, Gelesis100 is an effective and safe new nonsystemic therapy with a unique mechanism of action for overweight and obesity. Treatment doubles the odds of achieving clinically meaningful weight loss (≥ 5% and ≥ 10%). In addition, because of its highly desirable safety and tolerability profile, if approved, Gelesis100 could be considered a promising new therapy for the treatment of overweight and obesity.

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Gelesis is committed to responsible sharing of data from clinical trials we sponsor. This includes summary data and anonymized individual patient data as well as other information (e.g., protocols, clinical study reports). Requests from any qualified researchers who engage in rigorous, independent scientific research will be considered as long as the trials are not part of an ongoing or planned regulatory submission (this includes requests for data on unlicensed products and indications). Data will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on how to request access to the data, please email info@gelesis.com.

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