EP4.15 Early prediction of clinically significant weight loss with Gelesis200 in overweight and obesity in people with prediabetes or type 2 diabetes in the LIGHT-UP study

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OBJECTIVES

Early identification of future responders is widely used to minimize unnecessary exposure to risks and unnecessary expenses related to therapy with drugs or devices. Assessments that can predict long-term clinically meaningful weight loss can help tailor treatment for people with overweight or obesity.

A receiver operating characteristic (ROC) analysis was conducted on data from the LIGHT-UP study to identify the earliest timepoint for reliably predicting body weight (BW) Responders at 5% (≥ 5% BW loss from baseline at Week 25).

MATERIALS-METHODS

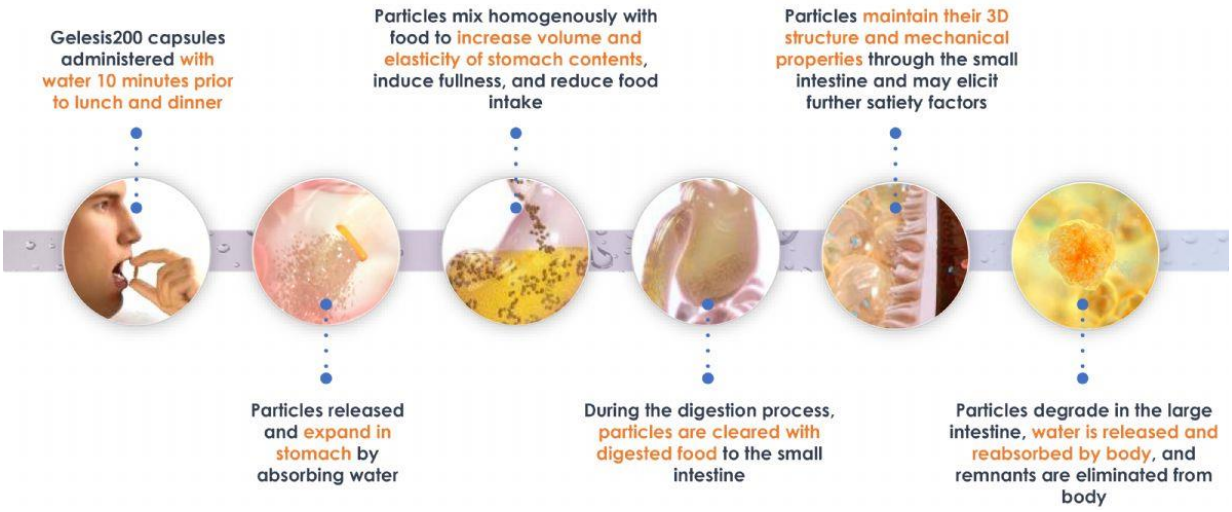
LIGHT-UP (NCT03058029), a multicenter, double-blind, randomized, placebo-controlled study, assessed the effects of Gelesis200, a non-systemic, investigational superabsorbent hydrogel, in people with a body mass index (BMI) between 27 and 40 kg/m2, with prediabetes (PD) or T2D (untreated or treated) over 25 weeks.

Participants were randomized to 2.10 g of Gelesis200 or placebo in capsules taken with water 10 minutes before lunch and dinner while given advice to support a 300 kcal/day energy-deficit diet with moderate-intensity physical activity (Figure 1).

A ROC curve was generated at each visit within each study arm (Gelesis200, placebo) by performing a logistic regression analysis. The percent weight loss from baseline for each visit was the independent variable, and whether that participant was a Responder at 5% at Week 25 was the dependent variable. The area under the curve (AUC) was then assessed. The maximum sensitivity and specificity were found at each visit by measuring off

the ROC curve at that visit. The earliest visit where the sensitivity and specificity were both at least 80% was then identified.

Figure 1



Gelesis200 hydrogel in the gastrointestinal tract.

RESULTS

The intention-to-treat population included 254 adults (males 40.2%, females 59.8%, mean age 49.6 years, mean BMI 34.7 kg/m2, PD 50.8%, untreated T2D 4.3%, treated T2D 44.9%) from 36 investigational sites in Europe and North America (Table 1).

Gelesis200 demonstrated a significant superiority over placebo in terms of weight loss.

ROC analysis showed that an early response to Gelesis200 treatment (≥ 2.6% weight loss from baseline) at Week 6 successfully predicted clinically meaningful weight loss (≥ 5% weight loss from baseline) at Week 25 (Figure 2 and Figure 3). Indeed, among people who lost ≥ 2.6% of BW from baseline at Week 6, 88% achieved ≥ 5% weight loss from baseline at Week 25 with a specificity of 85% (Table 2A). In the placebo arm, similar sensitivity and specificity for predicting meaningful weight loss was not achieved until sometime between Week 12 and Week 16 (Table 2B).

The overall incidence and severity of treatment-emergent adverse events (TEAEs) was similar between the 2 arms except for the incidence of constipation which was higher with Gelesis200 vs. placebo (14.3% vs. 3.9%) but with no severe cases (Table 3).

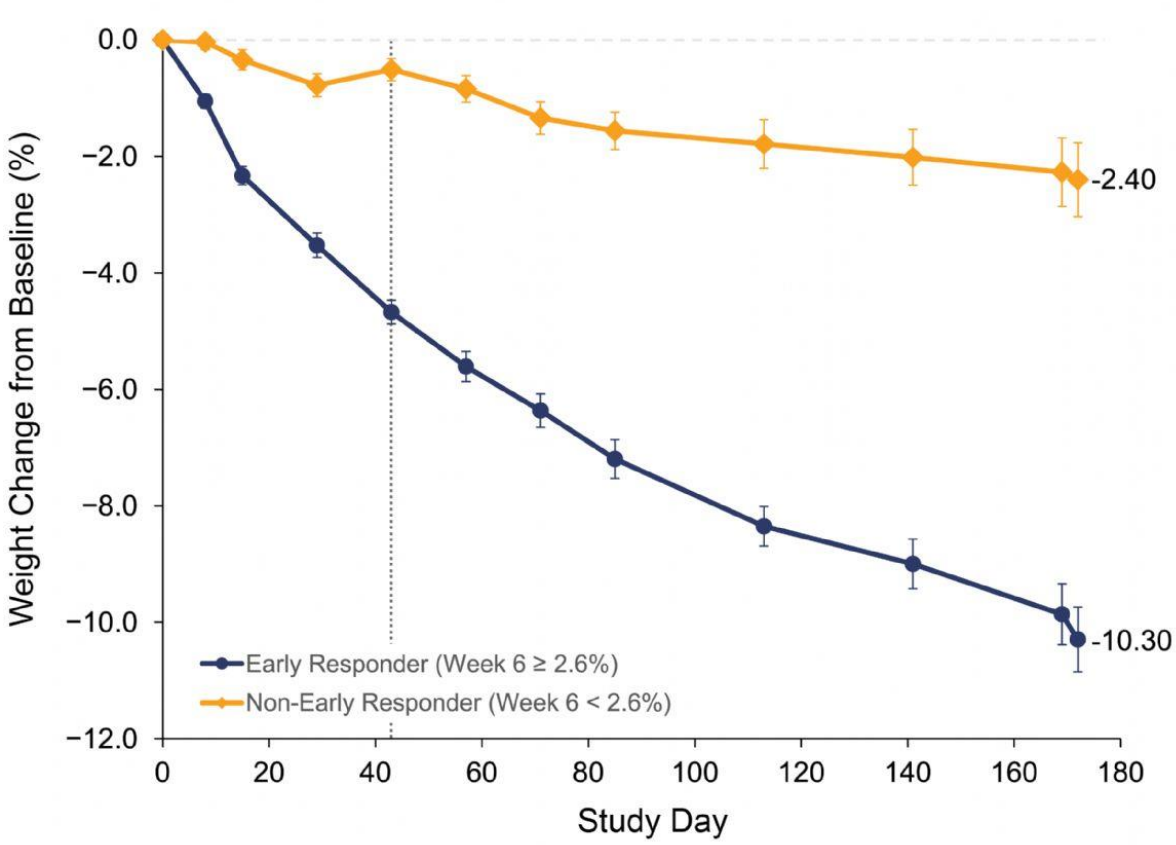
Table 1

Parameter	Gelesis200 (n = 127)	Placebo (n = 127)	*P* value
Female, n (%)	76 (59.8)	76 (59.8)	NS
Postmenopausal, n (%)	28 (22.0)	30 (23.6)	NS
Age (years)*	50.1 ± 10.7	49.1 ± 10.8	NS
BW (kg)*	100.7 ± 15.5	101.0 ± 17.4	NS
BMI (kg/m^2)*	34.8 ± 3.4	34.6 ± 3.4	NS
Overweight, n (%)	13 (10.2)	13 (10.2)	NS
Obese, n (%)	114 (89.8)	114 (89.8)	NS
WC (cm)*	114.3 ± 11.4	113.1 ± 12.4	NS
Current smokers, n (%)	23 (18.1)	19 (15.0)	NS
Dyslipidemia, n (%)	59 (46.5)	62 (48.8)	NS
Hypertension, n (%)	29 (22.8)	30 (23.6)	NS
PD, n (%)	63 (49.6)	66 (52.0)	NS
Untreated T2D, n (%)	6 (4.7)	5 (3.9)	NS
Treated T2D, n (%)	58 (45.7)	56 (44.1)	NS

N: Number of subjects; BW: Body weight; BMI: Body mass index; WC: Waist circumference; PD: Prediabetes; T2D: Type 2 diabetes; NS: Non-significant; *Mean ± SD.

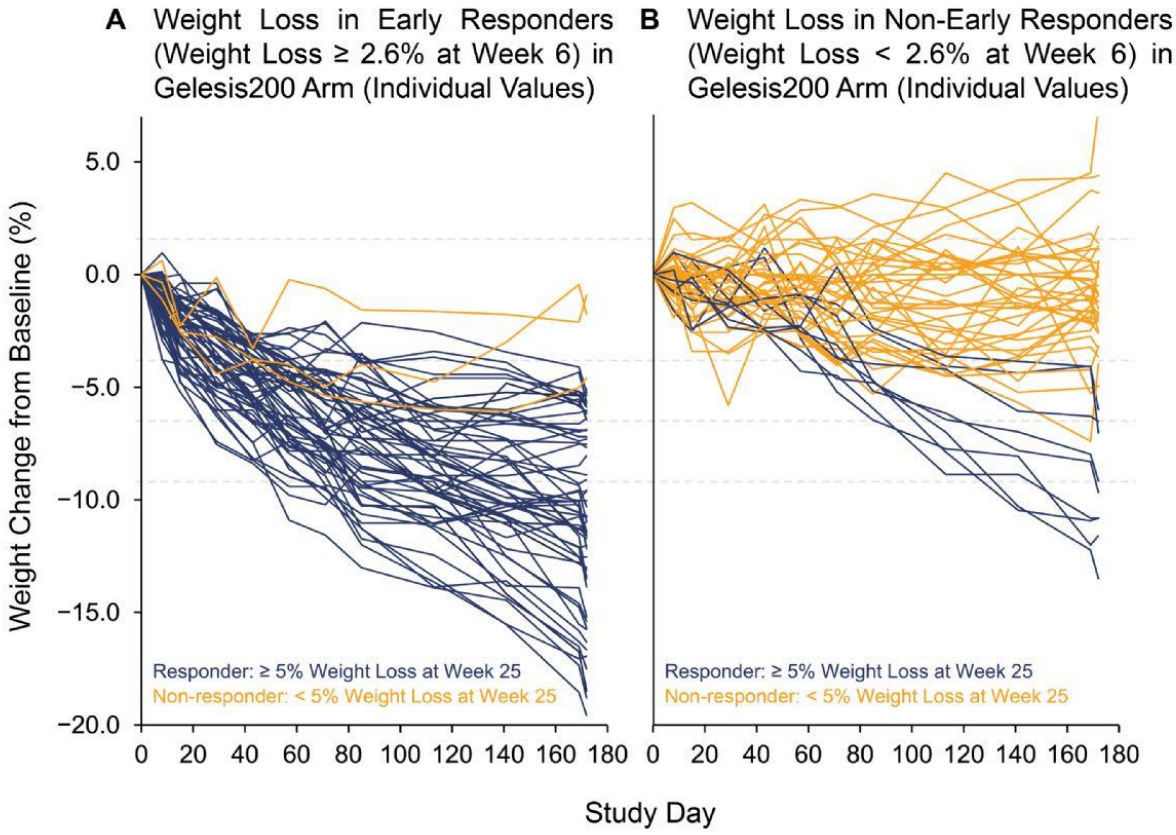
Baseline characteristics of the intention-to-treat population.

Figure 2



Weight loss in early responders and non-early responders in Gelesis200 arm (mean values).

Figure 3



Weight loss in early responders and non-early responders in Gelesis200 arm (individual values).

Table 2A

Time From Baseline (Week)	Weight Change (%)	Sensitivity	Specificity
Week 1	-0.45	0.72	0.63
Week 2	-1.30	0.68	0.68
Week 4	-1.90	0.75	0.75
Week 6	-2.56	0.88	0.85
Week 8	-2.75	0.87	0.88

ROC: Receiver operating characteristic.

ROC analysis for Responders at 5% in Gelesis200 arm.

Table 2B

Time From Baseline (Week)	Weight Change (%)	Sensitivity	Specificity
Week 1	-0.49	0.74	0.69
Week 2	-0.98	0.74	0.74
Week 4	-1.63	0.77	0.76
Week 6	-2.24	0.79	0.76
Week 8	-2.55	0.84	0.76
Week 10	-3.22	0.82	0.81
Week 12	-3.54	0.82	0.84
Week 16	-4.30	0.90	0.89

ROC: Receiver operating characteristic.

ROC analysis for Responders at 5% in placebo arm.

Table 3

Parameter	Gelesis200 (n = 126)	Placebo (n = 127)	*P* value
Any TEAEs, n (%)	79 (62.7)	79 (62.2)	NS
Any serious TEAEs, n (%)	5 (4.0)	2 (1.6)	NS
Infections and infestations, n (%)	37 (29.4)	35 (27.6)	NS
Gastrointestinal disorders, n (%)	36 (28.6)	30 (23.6)	NS
Musculoskeletal and connective tissue disorders, n (%)	16 (12.7)	14 (11.0)	NS
Nervous system disorders, n (%)	15 (11.9)	7 (5.5)	NS
Injury, poisoning and procedural complications, n (%)	8 (6.3)	8 (6.3)	NS
Vascular disorders, n (%)	8 (6.3)	4 (3.1)	NS
Investigations, n (%)	6 (4.8)	6 (4.7)	NS
Respiratory, thoracic and mediastinal disorders, n (%)	4 (3.2)	6 (4.7)	NS

TEAE: Treatment-emergent adverse event; N: Number of subjects; NS: Non-significant.

Overall TEAE profile and the most common TEAEs by system organ class in the safety population.

CONCLUSIONS

The results of AUC ROC analysis suggest that a weight loss of ≥ 2.6% as early as 6 weeks during treatment with Gelesis200 is highly predictive of clinically meaningful weight loss (≥ 5%) after 25 weeks.

The early prediction of clinically relevant weight loss outcome may allow early selection of people with overweight or obesity who will achieve successful weight loss with Gelesis200 and also potentially motivate treatment compliance.