Safety of Gelesis100 in Overweight or Obesity: Comprehensive Analysis of the GLOW Study

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DISCLOSURES

- Ken Fujioka has served as a paid consultant for Novo Nordisk, Eisai, Gelesis, KVK-tech, Amgen, Sunovion, Phenomix, Boehringer Ingelheim, Janssen Global Services and Roivant; has received research funding from Eisai; and has been a speaker for Novo Nordisk.

BACKGROUND AND OBJECTIVE

- When HCPs are surveyed as to barriers to prescribing weight loss medications, “safety concerns” are often cited as the number one reason.[1,2]
- Only 2% of patients with overweight or obesity receive anti-obesity drug therapy despite the overwhelming evidence of the growing burden of excess weight.[3,4]
- Gelesis100 (*brand name: Plenity™*) is a nonsystemic, superabsorbent hydrogel developed for the treatment of overweight or obesity.
    - Plenity is cleared for weight management in adults who are overweight or obese and have a BMI 25-40kg/m^2, when combined with diet and exercise.
- The **objective** of the GLOW study was to evaluate the safety and efficacy of Gelesis100 in patients with overweight or obesity, with and without type 2 diabetes (T2D).
- This presentation will focus on safety outcomes.

1. Granara B, Laurent J. J Am Assoc Nurse Pract. 2017; 29(9): 543-550.
2. Prospective Studies C, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. Lancet. 2009;373(9669):1083-96.
3. Xia Y, Kelton CM, Guo JJ, Bian B, Heaton PC. Obesity. 2015;23:1721-1728
4. Samaranayake NR, Ong KL, Leung RY, Cheung BM. Ann Epidemiol 2012;22:349-353.

GLOW STUDY DESIGN AND METHODS

6 Months

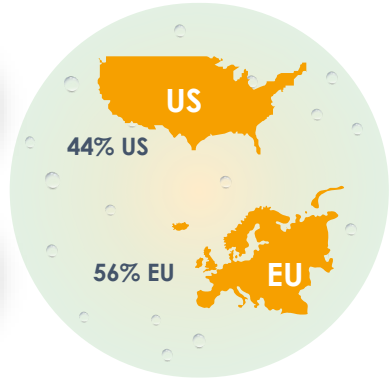
Multi-Center, Randomized, Double-Blind, 300 kcal/day deficit

Gelesis100
2.25 g BID
223 subjects

Lunch (**Gelesis100**), Dinner (**Gelesis100**)

Placebo*
213 subjects

Lunch (**Placebo**), Dinner (**Placebo**)



436 overweight and obese patients, including those with:

- Normoglycemia
- Prediabetes
- Type 2 diabetes

Co-Primary:

- Placebo-adjusted weight loss ≥ 3%
- Proportion of patients with weight loss of ≥ 5%

Secondary:

- Changes in key glycemic control parameters

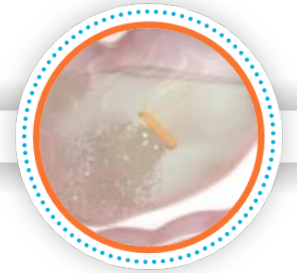
* Each capsule of placebo contained approximately 900mg of sucrose (less than 25 calories per day) and was taken with 500mL water

Greenway FL, Aronne LJ, Raben A, et al. A Randomized, Double-Blind, Placebo-Controlled Study of Gelesis100: A Novel Nonsystemic Oral Hydrogel for Weight Loss. *Obesity*. 2019;27(2):205-16.

HOW GELESIS100 IS TAKEN

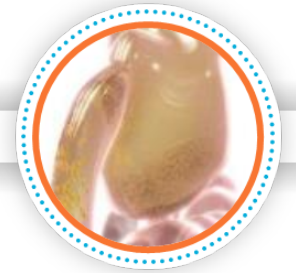
3 oral capsules administered **with 500ml of water 20-30 minutes** prior to lunch and dinner

Particles released and **expand (>100x) in stomach** by absorbing water



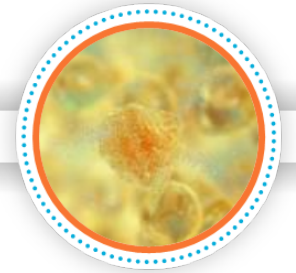
Particles mix with food to **increase volume and elasticity** of stomach contents

During the digestion process the particles are cleared with the digested food to the small intestine



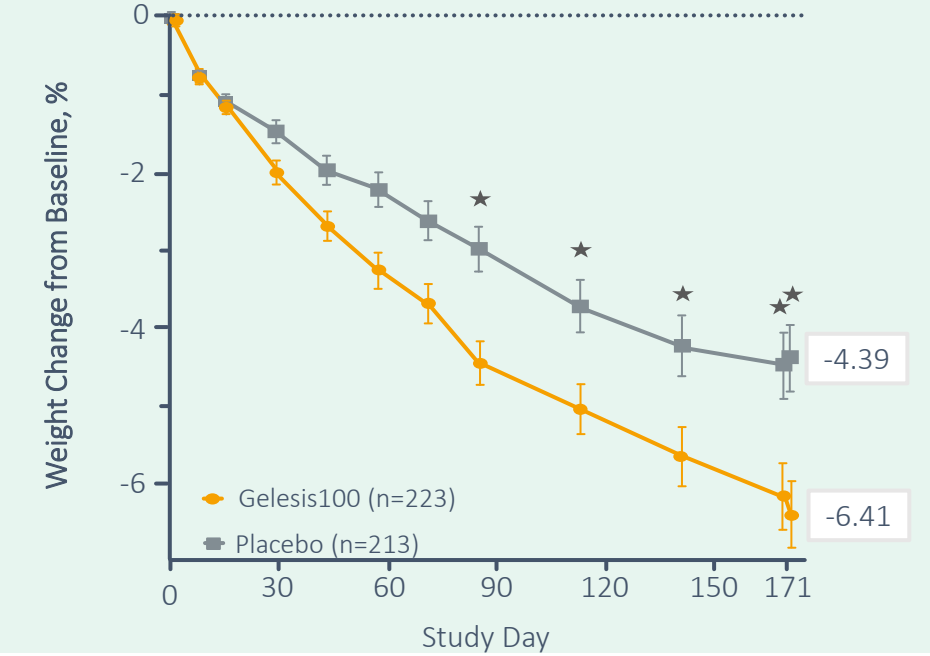
Particles **maintain their 3D structure** and mechanical properties through the small intestine and may elicit further satiety factors

Particles degrade in the large intestine, **water is released and reabsorbed** by body, and remnants are eliminated from body

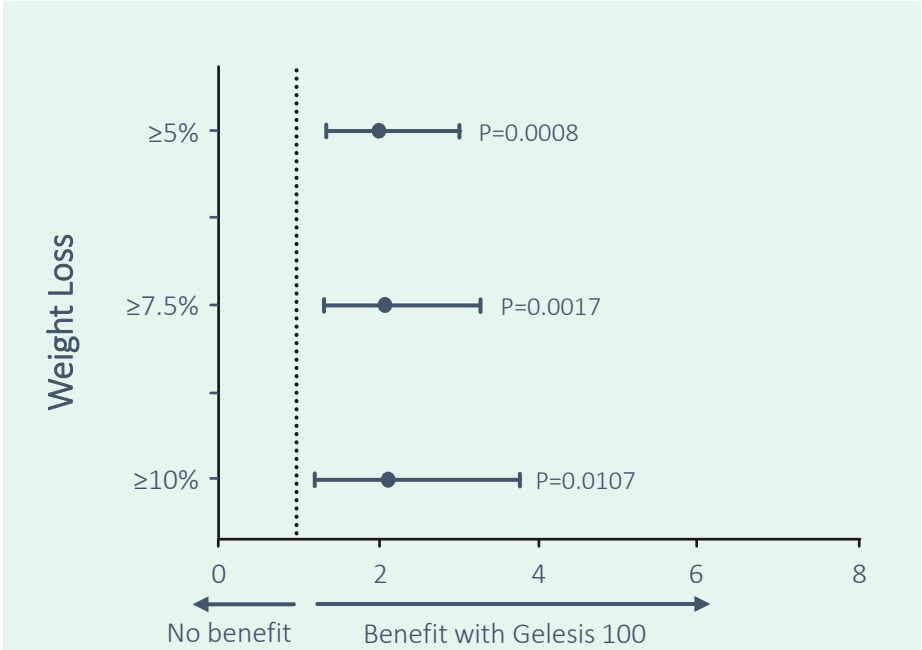


GLOW STUDY PRIMARY EFFICACY RESULTS

Weight Loss Over Time



Adjusted Odds Ratio and 95% Confidence Interval



- **Subjects assigned to Gelesis100 achieved significantly greater weight loss at 6 months (-6.4% vs. -4.4%, -2.1%, P=.0007, 95% CI -3.2 to -0.9), however this did not meet the predefined super-superiority margin of 3%.**
- **The adjusted odds ratio for achieving ≥ 5% weight loss was 2.0 (1.3-3.0), ≥ 7.5% was 2.1 (1.3-3.3), and ≥ 10% was 2.1 (1.2-3.8).**

*P < 0.05.

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RATES OF TREATMENT WITHDRAWAL WERE SIMILAR BETWEEN GELESIS100 AND PLACEBO

- Overall, 112 subjects failed to complete the treatment phase citing personal reasons as the most common cause for withdrawal.
- Fifteen subjects (8 in the Gelesis100 group, 7 in the Placebo group) withdrew from the study prior to the last dose due to adverse events (AEs).

PARAMETER	Gelesis100 (n)	Placebo (n)
Drop-out	23% (51)	29% (61)
Adverse events	3.6% (8)	3.3% (7)
Lost to follow-up	3.1% (7)	4.2% (9)
Protocol deviation	3.6% (8)	3.8% (8)
Other	2.7% (6)	1.4% (3)
Withdrawal by subject	9.9% (22)	16% (34)

SUMMARY OF ALL ADVERSE EVENTS IN GLOW

- No significant differences between the Gelesis100 group and Placebo group were observed in the overall rate of adverse events.
- There were no deaths reported in GLOW and there was only 1 serious adverse event (SAE) in the study, which was in the Placebo group.

PARAMETER	Gelesis100 (n)	Placebo (n)
% of subjects withdrew because of AE	3.6% (8)	3.3% (7)
% of subjects with any AE	71.3% (159)	70.6% (149)
% of subjects with severe AE	3.6% (8)	4.7% (10)
% of subjects with moderate AE	39.5% (88)	39.3% (83)
% of subjects with mild AE	55.6% (124)	55.5% (117)
# of subjects with serious AE	0	1*

*benign colon tumor, partial resection of colon, full recovery
AE = Adverse Event

OVERVIEW OF TREATMENT-RELATED ADVERSE EVENTS

- The overall occurrence of treatment-related adverse events was not significantly different between groups
- Gastrointestinal (GI)-related AEs were reported more frequently in the Gelesis100 group (P = 0.0248).

PARAMETER	Gelesis100 (n = 223)	Placebo (n = 211)	Difference (95% CI)	P-value
Any AE probably or possibly related	88 (39.5)	64 (30.3)	9.1 (–0.2, 18.2)	0.0557
Eye disorders	0 (0)	1 (0.5)	–0.5 (–3.0, 1.7)	0.4862
GI Disorders	84 (37.7)	58 (27.5)	10.2 (1.0, 19.1)	0.0248
General disorders	1 (0.4)	1 (0.5)	–0.0 (–2.6, 2.4)	1.0000
Infections and infestations	2 (0.9)	1 (0.5)	0.4 (–2.2, 3.1)	1.0000
Investigations	3 (1.3)	3 (1.4)	–0.1 (–3.3, 3.0)	1.0000
Metabolism and nutrition disorders	0 (0)	4 (1.9)	–1.9 (–5.1, 0.6)	0.0551
MSK and connective tissue disorders	2 (0.9)	0 (0)	0.9 (–1.5, 3.5)	0.4992
Nervous system disorders	4 (1.8)	2 (0.9)	0.8 (–2.2, 4.0)	0.6860
Renal and urinary disorders	1 (0.4)	0 (0)	0.4 (–1.8, 2.9)	1.0000
Reproductive disorders	0 (0)	1 (0.5)	–0.5 (–3.0, 1.7)	0.4862
Respiratory, thoracic disorders	1 (0.4)	1 (0.5)	–0.0 (–2.6, 2.4)	1.0000
Skin and subcutaneous disorders	1 (0.4)	3 (1.4)	–1.0 (–4.0, 1.7)	0.3599

INDIVIDUAL GASTROINTESTINAL ADVERSE EVENTS WERE SIMILAR BETWEEN GROUPS

PARAMETER	Gelesis100 % (n)	Placebo % (n)	*P* value
GI-related AEs*	37.7% (84)	27.5% (58)	0.0248
Abdominal distension	10.8% (24)	5.7% (12)	0.0579
Diarrhea	10.3% (23)	7.6% (16)	0.4015
Infrequent bowel movements	9.0% (20)	4.7% (10)	0.0910
Flatulence	8.5% (19)	4.7% (10)	0.1272
Abdominal pain	4.9% (11)	2.8% (6)	0.3258
Constipation	4.5% (10)	4.7% (10)	1.0000

- The most common gastrointestinal AEs in the Gelesis100 group were diarrhea, abdominal distension, infrequent bowel movements, flatulence, constipation, nausea, and abdominal pain.
- The occurrence of individual gastrointestinal AEs, regardless of their level of severity, was not statistically different between groups.

*Possibly or probably related

GASTROINTESTINAL ADVERSE EVENTS WERE MOSTLY MILD

- The majority of the Gastrointestinal events, deemed related, were assessed as mild.
- The GI events considered to be either moderate or severe were no different between groups.

	Gelesis100		Placebo			
Gastrointestinal Disorders	# of Events	% Patient with Event [% (n/N)]	# of Events	% Patient with Event [% (n/N)]	Difference (95% CI)	*P* value
All	158	37.7% (84/223)	105	27.5% (58/211)	10.2% (1.0%, 19.1%)	0.0248
Mild	119	32.3% (72/223)	83	24.2% (51/211)	8.1% (-0.7%, 16.7%)	0.0701
Moderate	35	9.0% (20/223)	20	7.1% (15/211)	1.9% (-3.8%, 7.4%)	0.4876
Severe	4	1.3% (3/223)	2	0.5% (1/211)	0.9% (-1.9%, 3.8%)	0.6238

GASTROINTESTINAL ADVERSE EVENT SUMMARY

	Gelesis100 (N=96 with GI AE)	Placebo (N=72 with GI AE)	Overall (N=168 with GI AE)
Days to GI AE*			
Mean ± SD (N)	31.3 ± 48.1 (186)	33.4 ± 42.5 (134)	32.2 ± 45.8 (320)
Median (Min, Max)	9.0 (0.0, 196.0)	12.0 (0.0, 182.0)	10.5 (0.0, 196.0)
Duration of GI AE			
Mean ± SD (N)	23.9 ± 41.5 (171)	12.4 ± 16.2 (122)	19.1 ± 33.8 (293)
Median (Min, Max)	7.0 (1.0, 202.0)	5.0 (1.0, 67.0)	6.0 (1.0, 202.0)
% of GI AEs That Resolved Within 14 Days	62.4% (116/186)	67.9% (91/134)	64.7% (207/320)
Action Taken in Response to GI AE			
No Change to Study Device Dose (%)	90.3% (168/186)	88.1% (118/134)	89.4% (286/320)
Study Device Dose Reduced (%)	4.8% (9/186)	6.7% (9/134)	5.6% (18/320)
Study Device Withdrawn or Suspended (%)	4.8% (9/186)	5.2% (7/134)	5.0% (16/320)

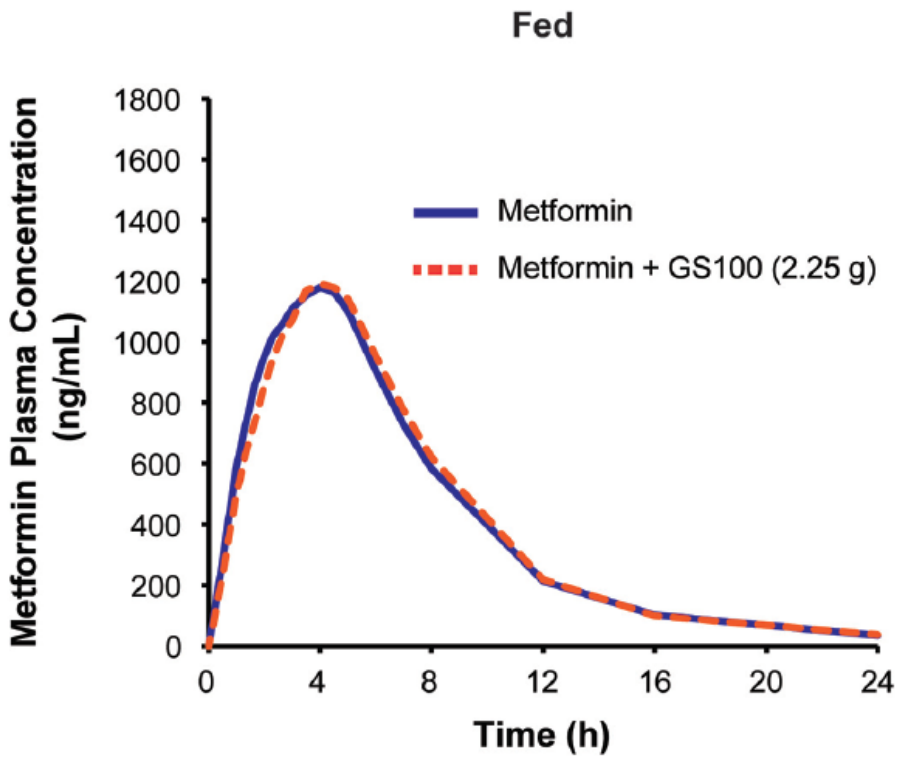
*GI AEs: Diarrhea, abdominal distension, infrequent bowel movements, flatulence, abdominal pain, and constipation

LABORATORY FINDINGS

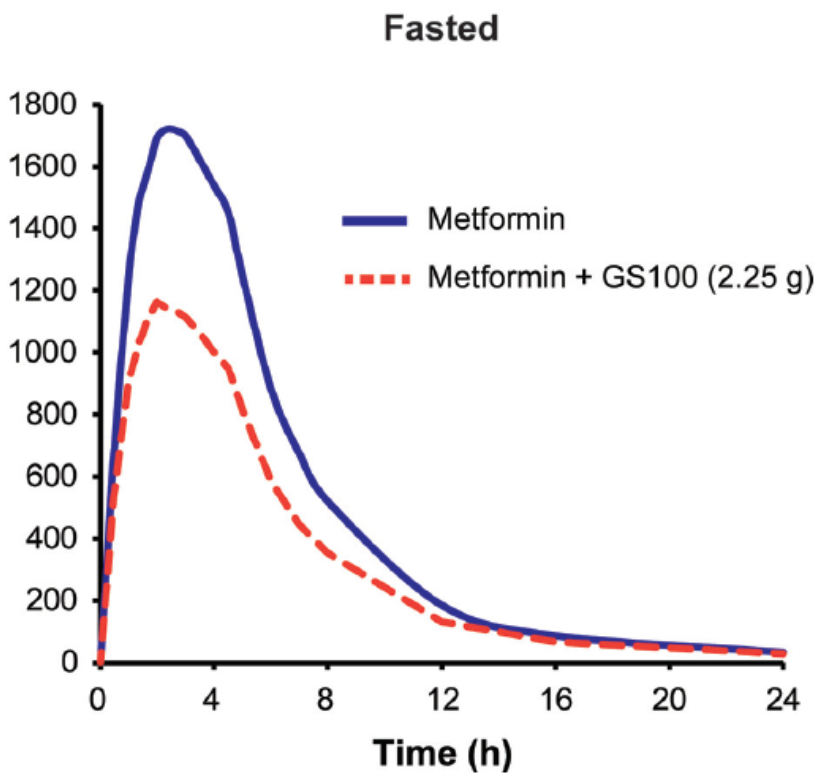
- No clinically meaningful abnormal hematology or chemistry findings, including serum sodium, potassium, calcium, and magnesium, were observed during the study.
- There were no significant differences in the serum levels of vitamins A, B1, B2, B6, B9, B12, D, and E between the two groups.
- There were no signals of altered absorption of medications based on TSH levels of subjects on thyroid replacement therapy, blood pressure management while on antihypertensives, LDL-C while on lipid-lowering agents, or blood glucose management while on metformin.

TSH = thyroid stimulating hormone, LCL-C = low-density lipoprotein-cholesterol

MEAN CONCENTRATION-TIME PROFILE FOR METFORMIN CO-ADMINISTRATION



Co-administration of metformin with Gelesis100 during a fed condition had no significant impact on C_{max}, AUC_{0-24}, and T_{max}.



Co-administration of metformin with Gelesis100 under fasting conditions altered metformin C_{max}, AUC_{0-24}, and T_{max} in a manner that was similar to that of the administration of metformin in the fed state.

C_{max} = peak plasma concentration, AUC_{0-24} = 24-hour area under the curve, T_{max} = time to peak plasma concentration

SUMMARY AND CONCLUSION

- The GLOW study was a randomized, controlled study of 6 months duration involving 436 subjects.
- 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.
- No clinically-meaningful changes were observed in hematology or chemistry.

Gelesis100 is a safe and well-tolerated therapy to aid in weight management of subjects with overweight or obesity.