Short-Term Administration of Gelesis200 Increases Fullness and Satiety in Overweight and Obese Subjects: First-in-Human Safety Study

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ABSTRACT

Background:
• Gelesis100, a novel biocompatible hydrogel, increases satiety, reduces food intake, and induces weight loss when taken 30 min before meals. Gelesis200, an additional hydrogel in the product family with a higher elastic modulus and a faster hydration rate, is being developed for weight loss and glycemic control, particularly in subjects with prediabetes and type 2 diabetes.

Methods:
• Gelesis200 (2.10 g) or placebo capsules were administered to 24 overweight and obese male subjects 10 or 30 min before standard meals on a single day, in a double-blind, crossover fashion. Appetite was assessed using visual analogue scales (VAS). All subjects completed VAS after breakfast and lunch and 12 subjects also completed VAS after dinner. Results are differences in incremental area under the curve and individual timepoints.

Results:
• Gelesis200 was safe and well tolerated. Compared to placebo, administration of Gelesis200 at -10 min resulted in greater fullness after lunch (180 ± 398 cm²/min; P = 0.046). The 12 subjects who completed all 3 meals had greater fullness during the entire day (704 ± 839 cm²/min; P = 0.012). Administration of Gelesis200 at -10 min resulted in greater satiety just before dinner (2.3 ± 2.8 cm; P = 0.017) and 150 min (1.4 ± 2.1 cm; P = 0.032) and 180 min (1.5 ± 2.0 cm; P = 0.031) after dinner. When administered at -30 min, the above differences with placebo were not observed. Compared to administration at -30 min, administration at -10 min produced more fullness 90 min after lunch (1.0 ± 2.5 cm; P = 0.005) and less desire to eat 30 min (-0.8 ± 1.7 cm; P = 0.037), 90 min (-1.3 ± 2.0 cm; P = 0.005), and 120 min (-1.0 ± 2.1 cm; P = 0.039) after lunch, consistent with faster hydration kinetics of Gelesis200.

Conclusions:
• Short-term administration of Gelesis200 to overweight and obese subjects was safe and well tolerated. Administration 10 min before meals increased fullness and satiety, supporting the utility of Gelesis200, a rapidly acting hydrogel, in the management of obesity.

REFERENCES


7. Yishai Zohar1 and Hassan M. Heshmati1

8. lorien.urban@gelesis.com

9. Poster presented at Obesity Week 2016, October 31 - November 4, New Orleans, LA Poster number: T-P-LB-3652

CONCLUSIONS

• Short-term Gelesis200 administration in this first-in-human study was safe and well tolerated.

• Administration of Gelesis200 10 min before meals increased subjective feelings of fullness and satiety which is consistent with faster hydration kinetics.

• Taken together, these data support further studies on chronic administration of Gelesis200, a rapidly acting hydrogel, in the management of obesity.

BACKGROUND

• Obesity is a major predisposing factor for prediabetes, type 2 diabetes, and other comorbidities. The worldwide prevalence of obesity has nearly doubled between 1980 and 2014 according to World Health Organization estimates.1

• Concomitant with this rise in obesity, the number of adults with diabetes worldwide has quadrupled since 1980.2 In fact, 85% of people with type 2 diabetes are overweight or obese.3

SUBJECTS

• 24 healthy males with BMI 27-35 kg/m² and fasting plasma glucose between 90 and <126 mg/dL were enrolled.
• Incremental area under the curve (iAUC) was calculated using the linear trapezoidal method on baseline corrected data. Baseline was defined in one of three ways:

- Intracluster area under the curve (iAUC) was calculated using the linear trapezoidal method on base-line corrected data. Baseline was defined in one of three ways:
  - 10 min before breakfast for comparisons where treatment was administered 10 min prior to meals (arms A and C)
  - 30 min before breakfast for comparisons where treatment was administered 30 min prior to meals (arms B and D)
  - 0 min before breakfast for comparisons where treatment was administered 30 min prior to meals (arms A and B)

• Scheduled times were used in the calculation of the linear trapezoidal method on base-line corrected data. Baseline was defined in one of three ways:

- 10 min before breakfast for comparisons where treatment was administered 10 min prior to meals (arms A and C)
- 30 min before breakfast for comparisons where treatment was administered 30 min prior to meals (arms B and D)
- 0 min before breakfast for comparisons where treatment was administered 30 min prior to meals (arms A and B)

• The most common AEs were headache (9%), hot flush (5%), somnolence (5%), and pruritic dermatitis (4%).

• Because ingested Gelesis200 is non-systemic and acts entirely within (and is ultimately excreted by) the gastrointestinal (GI) system, GI AEs were examined separately.

SAFETY AND TOLERABILITY

- Gelesis200 was safe and well tolerated. The total number of adverse events (AEs) was similar between Gelesis200 and Placebo (Table 2). Nearly all AEs were mild in intensity (Table 3), and no AEs were regarded as being probably related to treatment (Table 4). There were no serious AEs.

- The most common AEs were headache (9%), hot flush (5%), somnolence (5%), and pruritic dermatitis (4%).

- Because ingested Gelesis200 is non-systemic and acts entirely within (and is ultimately excreted by) the gastrointestinal (GI) system, GI AEs were examined separately.

Table 2: GI and Other AEs by Treatment Arm and Pooled.

<table>
<thead>
<tr>
<th>AE Intensity</th>
<th>Treatment Arm</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
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<tr>
<td>Severe</td>
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</tbody>
</table>

Table 4: AE Causality by Treatment Arm and Pooled.

<table>
<thead>
<tr>
<th>AE Causality</th>
<th>Treatment Arm</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly</td>
<td></td>
<td></td>
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<tr>
<td>Probably</td>
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</table>

Table 5: Incremental AUC for Fullness and Satiety When Gelesis200 or Placebo Was Administered 10 Min Prior to Meals.

<table>
<thead>
<tr>
<th>Fullness (Mean ± SD)</th>
<th>P values</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Gelesis200 Placebo</td>
<td></td>
</tr>
<tr>
<td>Breakfast</td>
<td></td>
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<tr>
<td>Lunch</td>
<td></td>
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<tr>
<td>Dinner</td>
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</table>

DISCUSSION

• Despite well-documented benefits of weight loss on obesity-related comorbidities, adoption of antiobesity pharmacotherapies is lagging likely due to safety concerns based on history of FDA withdrawals. This highlights an unmet need for safe and effective therapies to facilitate the reduction of excess weight.

• Administration of Gelesis200 10 min prior to meals induced subjective feelings of fullness and satiety. This is consistent with previously reported appetite effects of Gelesis100. However, administration of Gelesis200 at 10 min prior to lunch was better at producing prosystemic fluid intake (i.e., desire to eat) than administration 30 min prior to lunch with its consistent with the faster hydration kinetics of Gelesis200.

• Gelesis200, is similar in concept to Gelesis100, but has different physical properties that could potentially address different indications and treatment regimens. Gelesis200 hydrates more rapidly than Gelesis100 and creates a higher elastic response and viscosity, but occupies a slightly smaller volume in the stomach. For example, due to its higher elastic response and accelerated hydration, Gelesis200 could be more suitable for glycemic control, where one relevant mechanism is the delay of the absorption of glucose in the small intestine. For this purpose, the volumetric effect at the beginning of the meal could be less important and Gelesis200 could be administered immediately prior to the meal. These properties could make Gelesis200 more suitable for glycemic control in subjects with prediabetes and type 2 diabetes, who may or may not require weight loss.

• In this study, Gelesis200 was safe and well tolerated. Overall, AEs were mild in intensity, were similar in frequency between Gelesis200 and Placebo treatment arms, and no AEs were regarded as being probably related to treatment.

• Given the overall benefit-risk profile observed in this first-in-human study, further studies on chronic administration could be promising.