

# Ghrelin Agonist TZP-101 Improves Symptoms and Gastric Emptying in Diabetic Patients with Gastroparesis

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## 1. Background

Diabetic gastroparesis affects 30-50% of patients with diabetes and impacts nutrition, weight management, and glycemic control. Patients with gastroparesis present with a spectrum of symptoms that include nausea, vomiting, postprandial fullness/early satiety, and loss of appetite. Nausea, vomiting, and early satiety are present in approximately 90%, 70-80% and 60-80% of these patients, respectively.<sup>1,2</sup> New treatment options for moderate to severe gastroparesis are needed.

TZP-101 is a macrocyclic peptidomimetic ghrelin receptor agonist with a prolonged half-life and enhanced metabolic stability and affinity for the growth hormone secretagogue receptor (GHS-R1a) compared to the endogenous ligand ghrelin.<sup>3,4,5</sup> TZP-101 accelerates gastric emptying in adults with diabetic gastroparesis and also improves gastrointestinal recovery in patients with postoperative ileus following abdominal surgery.<sup>6,7</sup>

## 2. Objectives

A placebo-controlled, randomized, double-blind study evaluated the safety and efficacy of repeat dosing of TZP-101 in patients with moderate to severe symptoms of diabetic gastroparesis.

## 3. Study Design and Patient Characteristics

**Eligibility:** Adult men and women with type 1 or 2 diabetes mellitus and diagnosis of gastroparesis.

**Randomization:** performed using adaptive design.

**Treatment:** Daily 30-min IV infusions of placebo or TZP-101 (20, 40, 80, 160, 320, or 600µg/kg) for 4d.

**Endpoints and Assessments:** 1) Improvement in symptoms as reported by patients using the Gastroparesis Cardinal Symptom Index (GCSI) scale where: 0=none, 1=very mild, 2=mild, 3=moderate, 4=severe and 5=very severe assessed daily during dosing and 30 days after treatment; 2) Changes in gastric emptying measured by scintigraphy; 3) Correlation of baseline characteristics and improvements in GCSI.

Baseline/screening Parameter	TZP-101 Concentration (µg/kg)						
	Placebo n=19	20 n=8	40 n=17	80 n=13	160 n=6	320 n=6	600 n=7
- Age, yr.	45.7±12.6	41.4±12.5	43.4±15.1	44.0±11.0	47.2±11.2	40.8±13.7	48.4±13.8
- Men/women, %	47/53	25/75	29/71	23/77	33/67	33/67	29/71
- White, n (%)	18 (95)	7 (88)	17 (100)	12 (92)	6 (100)	6 (100)	7 (100)
- BMI, kg/m <sup>2</sup>	27.5±5.1	26.3±5.2	26.3±6.0	27.7±5.8	26.9±3.5	30.0±3.8	25.6±4.2
- Diabetes, yr.	18.9±12.4	18.0±9.1	22.3±9.1	17.6±12.4	20.7±10.7	21.7±10.7	30.9±18.0
- Gastroparesis, yr.	6.1±7.1	2.9±2.2	4.1±3.5	7.2±8.4	4.5±4.6	4.5±4.6	2.1±2.0
- HbA1c, %	8.0±1.6	9.1±2.7	8.1±1.9	8.6±1.7	8.4±1.2	9.2±2.1	9.4±1.5
- Neuropathy*	2.11±1.33	2.75±1.28	2.24±0.75	1.92±1.04	2.33±0.82	2.17±1.33	1.86±1.35
- GE-scintigraphy	153.0±28.6	154.7±18.2	159.3±61.1	170.5±75.0	127.4±10.4	184.0±66.6	122.8 (n=1)
- GE-breath test min**	168.6±67.8	186.0±32.7	172.4±66.6	161.6±46.1	141.0±27.4	162.0±15.1	139.3±16.4
- Total GCSI score	3.7±0.7	3.5±0.6	3.5±0.5	3.5±0.7	3.7±0.7	3.7±0.6	3.6±0.6
- Fullness/satiety	3.9±0.7	3.8±0.6	4.0±0.7	3.7±1.0	3.9±0.5	3.5±0.7	3.4±1.2

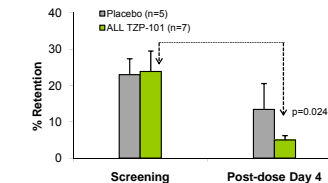
\*Level of autonomic function/neuropathy was determined on a scale from 0-4, with a zero indicating normal function and a 4 indicating abnormal function for orthostatic hypotension and beat-to-beat variation.

\*\*Gastric half-emptying time determined after ingestion of a radio-labeled meal (ULN = 135 min) or using the acetate breath test (ULN -100 min).

## 4. Results

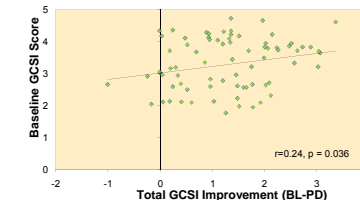
### 5. Improvement in Gastric Emptying after 4 Days of TZP-101:

➤ Subset study of twelve subjects (n=5 placebo, n=7 TZP-101) who had scintigraphy performed the day after the last dosing day.  
➤ After 4 daily doses of TZP-101, gastric emptying was normalized at 4 hrs (<10% retention) in all patients and this result was statistically significantly different from baseline.



### 6. Correlation of Baseline Characteristics and GCSI Improvements:

➤ Improvements in GCSI following TZP-101 dosing correlated with the degree of symptom severity at baseline.  
➤ Other baseline characteristics did not correlate with GCSI improvement, including:  
a) gastric emptying half-emptying time at screening  
b) screening HbA1C  
c) diabetes type  
d) age and sex  
e) mean blood glucose levels across dosing days



**7. Safety and Tolerability:** Safety profiles were similar in the placebo and TZP-101 groups and all doses appeared to be well tolerated.

## 5. Conclusions

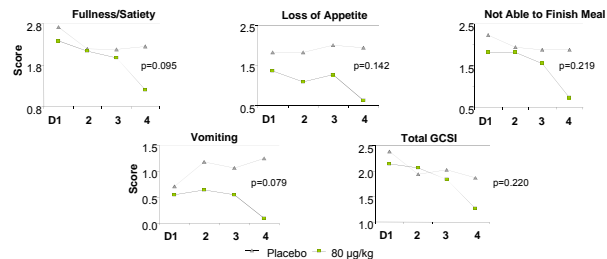
- TZP-101 for 4 days in patients with diabetic gastroparesis reduced or improved post-prandial fullness, loss of appetite, and vomiting, with evidence of sustained reduction over 30 days.
- Gastric emptying was normalized after treatment with TZP-101 for 4 days.
- Improvement in gastric emptying and gastroparesis symptoms is particularly relevant for diabetic patients since these factors contribute to impaired glycemic control, malnutrition, poor health-related outcomes, and decreased quality of life.
- Further investigations are warranted to confirm TZP-101 efficacy in managing critical symptoms of gastroparesis.

References  
1) Søjbjerg I et al. Dig DisSci 1998; 43:2398 2) Hoogerwerf WA et al. Am J Gastro 1999; 94:1029 3) Fraser G et al. Endocrinol 2008;149:620  
4) Lassiter KC et al. J Clin Pharmacol 2008;48:193 5) Wargin W et al. Clin Drug Investig 2009;29:400 6) Ejlskjær N et al. Aliment Pharm Ther 2009;29:1179  
7) Popescu I et al. Dis Colon Rectum 2009; In Press.

### 1. Dose Selection:

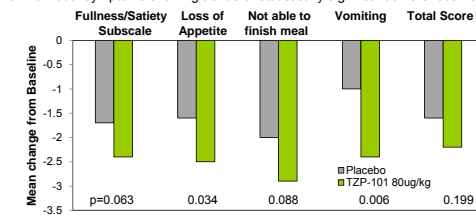
The 80 µg/kg dose was identified as the most effective dose based on Bayesian analysis of the 4-day mean change from baseline for the GCSI Postprandial Fullness/ Early Satiety subscale score (primary endpoint for the study).

**2. GCSI Symptom Improvement Across Dosing Days:** GCSI scores for Days 1-4 of dosing. Patients in the 80 µg/kg TZP-101 group had a greater rate of decline in their scores and improvement of symptoms over time than the placebo group. P values are shown for slope differences.



### 3. GCSI Symptom Improvement at End of Dosing (Day 4):

Change from baseline (some negative numbers indicate improvement) in GCSI scores for subscales or individual symptoms showing trends or statistically significant differences from placebo.



### 4. Sustained Improvement in Vomiting Scores at 30-day Follow-up:

➤ 60% of pts in the TZP-101 80 µg/kg group had >50% improvement in vomiting at the 30-day follow-up compared to 15% of pts in the placebo group (p=0.039).  
➤ Sustained improvements in other symptoms were numerically greater in the TZP-101 group than placebo, but differences were not statistically significant.

