

Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic gastroparesis

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SUMMARY

Background

TZP-101 is a synthetic, selective ghrelin agonist in development for gastroparesis.

Aim

To assess safety and effects of TZP-101 in diabetes patients with symptomatic gastroparesis.

Methods

Adults with type 1 or type 2 diabetes mellitus received placebo and TZP-101 (80, 160, 320 or 600 µg/kg) infusions in a cross-over manner following a radiolabelled meal. Blood glucose levels were stabilized using a hyperinsulinemic-euglycemic clamp. Primary endpoints were gastric half emptying and latency times. Secondary measures included assessment of gastroparesis symptoms and endocrine responses.

Results

Ten patients with type 1 ($n = 7$) or 2 ($n = 3$) diabetes, moderate-to-severe gastroparesis symptoms and $\geq 29\%$ retention 4 h after a radiolabelled solid meal were enrolled. TZP-101 produced significant reductions in solid meal half-emptying (20%, $P = 0.043$) and latency (34%, $P = 0.037$) times vs. placebo. Reductions in overall postmeal symptom intensity (24%) and postprandial fullness (37%) following TZP-101 infusion were not statistically significant. Most adverse events were mild and self-limiting and there were no identifiable differences in numbers or types of adverse events between TZP-101 and placebo.

Conclusions

This proof-of-concept study demonstrates that the ghrelin agonist TZP-101 is well-tolerated in diabetes patients with moderate-to-severe chronic gastroparesis and shows statistically significant improvements in gastric emptying.

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INTRODUCTION

Gastroparesis is a chronic disorder of gastric motility characterized by delayed gastric emptying in the absence of mechanical obstruction accompanied by gastrointestinal symptoms including postprandial fullness, nausea and vomiting, bloating, early satiety and epigastric pain or discomfort. The cause of gastroparesis is often unidentified, but it is associated with other medical conditions including diabetes mellitus. Among 146 community-based participants and outpatients with gastroparesis, 29% of cases occurred in patients with diabetes.¹ Chronic abnormal gastrointestinal symptoms diminish quality of life in diabetes patients.² Slow gastric emptying, which occurs in 30–50% of patients with type 1 or type 2 diabetes [reviewed in³], contributes to poor nutrition, poor glycaemic control and reduced oral drug absorption.⁴

Current treatment options for gastroparesis remain limited and include dietary modifications, and prokinetic and antiemetic therapy. A significant percentage of gastroparesis patients require continuous prokinetic treatment,^{1,5} despite central nervous system side effects associated with many of the currently available drugs.⁶ Patients with severe gastroparesis who fail conventional therapies may undergo radical gastrointestinal surgery (e.g. gastrostomy, jejunostomy) and invasive procedures (e.g. gastric electrical stimulation) that must be performed in specialty gastroenterology units.^{7,8} While these procedures are reserved for seriously disadvantaged patients,⁹ there are limited data addressing outcomes and patient acceptance of these procedures.¹⁰

To address the unmet need for treating severe gastroparesis, compounds are in development that target novel pathways to stimulate gastric motility. Ghrelin is the natural ligand for the growth hormone secretagogue receptor (GHSR) and is locally produced in gut mucosa.¹¹ Ghrelin stimulates neural signalling in the gastrointestinal tract to promote motility¹² and produces a gastroprokinetic response in individuals with gastroparesis.^{13–15} When injected, ghrelin has a very short half-life¹⁶ limiting its therapeutic potential. The synthetic, selective ghrelin agonist TZP-101, which has a prolonged half-life¹⁷ and enhanced metabolic stability and affinity for the human GHSR type 1a compared to ghrelin, shows gastroprokinetic activity in animal models¹⁸ and is well-tolerated in healthy subjects administered single doses.¹⁷ The primary objective of the present proof-of-concept study was to

assess the safety and effects of TZP-101 on gastric emptying in diabetes patients with symptomatic gastroparesis.

METHODS

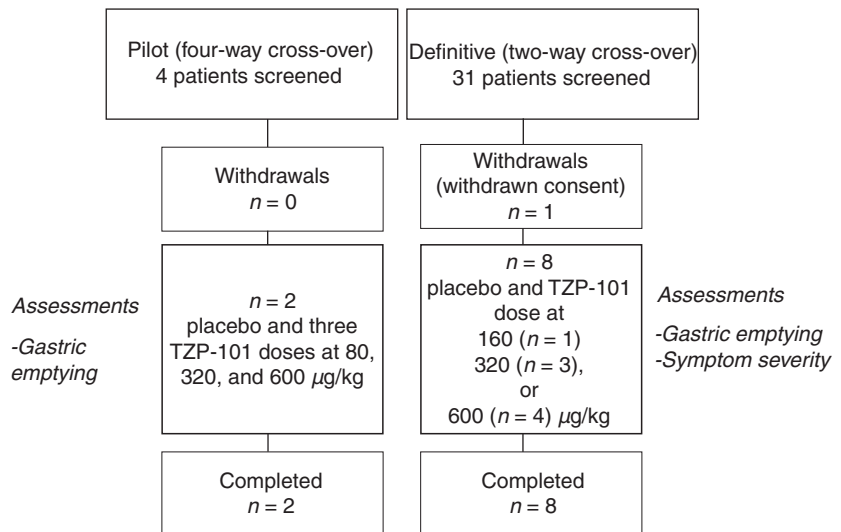
Men and women, aged 18–65 years with type 1 or type 2 diabetes mellitus and diagnoses of gastroparesis were enrolled in a double-blind, randomized, placebo-controlled, single-dose, cross-over study conducted at two centres in Denmark and one centre in Sweden from October 2006 to July 2007 (registry #NCT0063908) according to conditions of the Declaration of Helsinki, Amendment 5 (October 2000). Independent Ethics Committees (The Scientific Ethics Committees for the Municipalities of Copenhagen and Frederiksberg; the Regional Investigational Board, Stockholm) approved the protocol and all patients provided written informed consent.

Study design

Screening and eligibility. Eligible patients had normal upper endoscopy results, no serious co-morbid conditions, gastroparesis characterized by gastric retention $\geq 60\%$ at 2 h and $\geq 10\%$ at 4 h after a solid radiolabelled meal and at least a 3 month history of chronic upper abdominal discomfort with two or more of the following symptoms: postprandial fullness, bloating, epigastric discomfort, early satiety, belching after a meal, nausea and/or vomiting. Use of medications either accelerating or delaying gastric motility was permitted if patients took stable doses for at least 1 month prior to screening and continued through discharge. Postmenopausal or permanently sterilized women were enrolled. Exclusion criteria included use of any investigational drug within the preceding 30 days.

At screening, patients rated the severity of gastrointestinal symptoms during the previous 2 weeks using the Gastroparesis Cardinal Symptom Index (GCSI) from none (=0) to very severe (=5) on a 6-point scale.¹⁹ Patients completed the Michigan Neuropathy Screening Instrument (MNSI)²⁰ and had cardiovascular autonomic neuropathy measurements that included beat-to-beat heart rate variation (abnormal defined as a difference ≤ 10 beats/min in a supine patient breathing 6 times/min) and orthostatic hypotension evaluation (abnormal defined as a fall in systolic BP of ≥ 30 mmHg 2 min after standing). Other screening

Figure 1. Disposition of patients, interventions and assessments in the pilot (four-way cross-over) and definitive (two-way cross-over) phases of the study.



assessments included haematology and clinical chemistry (including HbA1c).

Interventions and study visits. The study was conducted in two phases: an initial pilot phase and a second definitive phase as summarized in Figure 1. During the pilot phase, patients received 30 min intravenous (IV) infusions of TZP-101 (80, 320, and 600 µg/kg provided by Tranzyme Pharma) and placebo following a test meal (described below) in a 4-way cross-over manner. The TZP-101 doses were selected based on the safety and tolerability data from a dose escalation study in healthy volunteers.¹⁷ Data from the two patients dosed in the pilot phase of the study showed that TZP-101 administration resulted in an average reduction in half-emptying time of 25%. The emptying improvement did not follow a dose proportional pattern and it appeared that the dose response curve may be bell-shaped. Therefore, data from the pilot phase were used to implement a dose-adjustment paradigm in the definitive study phase. During the definitive phase, patients received IV infusions of one TZP-101 dose and placebo after a test meal in a two-way cross-over design. The dose-adjustment paradigm was as follows: the first three patients received 600 µg/kg TZP-101. If a $\leq 25\%$ reduction in half-emptying time occurred, the TZP-101 dose was decreased to 320 µg/kg for the next three patients. The paradigm anticipated TZP-101 dose ranges of 20–600 µg/kg. Successive dosing was not implemented until safety and tolerability data from the previous dosing set were reviewed.

A hyperinsulinemic-euglycemic clamp technique²¹ was used to secure stable blood glucose levels between

6 and 8 mmol/L prior to, during and 4 h after dosing in both phases of the study. Patients arrived at the clinic the evening before scheduled dosing and remained in the clinic for 24 h following each dosing event. Seven days later, patients returned to the study centre for cross-over treatment. A follow-up visit was made 3 days after the last dosing. Group assignments and study interventions are shown in Figure 1. Patients and all study staff were blinded to treatment assignments.

All patients received a standardized low fat meal that was calculated per the individual patient's caloric intake requirements the evening before dosing and then fasted overnight for 10 h prior to gastric emptying assessments. Gastric emptying was evaluated using scintigraphy and a 282 kcal ^{99m}Tc-stannous colloid-labelled egg sandwich meal (two scrambled eggs, two pieces of toasted bread) and 300 mL of water containing ¹¹¹In-DTPA as described by Guo *et al.*²² Gastric emptying was measured at baseline, immediately after meal ingestion and at 30, 60, 120, 180 and 240 min after meal ingestion.

Endpoints. The primary end point was gastric half-emptying time of the radiolabelled solid meal. Secondary gastric emptying endpoints were solid and liquid latency times (time required for the first 5% of the meal contents to leave the stomach) and liquid half-emptying time.

Symptom relief was assessed during the definitive phase using a gastroparesis symptoms assessment (GSA)¹⁴ completed by patients before the meal, at the start of dosing, and then every 30 min for 4 h. Patients rated the intensity of epigastric pain, bloating,

postprandial fullness, nausea, belching, and epigastric burning on a 4-point scale from 0 (absent) to 3 (severe). An overall GSA score, ranging from 0 to 18 was obtained by adding the six individual symptom scores.

Blood samples were collected during the definitive phase to evaluate ghrelin, growth hormone (GH), insulin-like growth factor (IGF-I) and pancreatic polypeptide (PP) concentrations prior to infusion and up to 24 h after the start of the infusion.

Analytical assays. Serum and plasma samples were collected at 0, 15, 45, 90, 180 and 360 min, and 12 and 24 h after dosing in the eight patients in the definitive phase. Samples were prepared as previously described for GH, IGF-I, ghrelin and PP assays.¹⁷ For GH, IGF-1 and PP, a serum sample was prepared by allowing the blood to clot at room temperature for 30–45 min, followed by centrifugation at 3000 rpm for 15 min at 4 °C and storage of serum at –70 °C. For ghrelin, a plasma sample was prepared by collecting the blood in an EDTA tube, incubating for up to 30 min, followed by centrifugation at 3000 rpm for 15 min at 4 °C and storage of plasma at –70 °C. Ghrelin plasma concentrations were determined by a radioimmunoassay as previously described.²³ GH and IGF-I serum concentrations were determined by chemiluminescence enzyme immunoassays and PP serum concentrations by radioimmunoassay (Cario Diagnostic A/S., Copenhagen, Denmark). Venous blood glucose was measured by the glucose dehydrogenase method (Accucheck Inform, Roche Diagnostics, Hvidovre, Denmark).

Safety. Vital signs, 12-lead electrocardiograms (ECG) and adverse events were recorded during the 24-h post-dose periods in the clinic and at follow-up. Haematology and clinical chemistry assessments were made at the follow-up visit. All randomized patients who received at least one dose of study medication were evaluated for safety.

Statistical analyses

Results are expressed as means \pm S.E.M. An enrolment of 10 patients was established to provide 80% power to detect a 1-sigma treatment effect (a mean difference between treatments equal in magnitude to the standard deviation of the paired differences) for any continuous gastric-emptying endpoint. Dose effects were analysed

by a linear mixed-effects model in which the value of the efficacy endpoint was modelled as a function of the dose group (fixed), with a separate intercept for each subject (random). A significance level of 0.05 was used in all analyses.

Half-emptying and latency times were obtained from regression analysis of gastric emptying data using a 'power-exponential' model.²⁴

Cumulative GSA Scores (overall and individual symptom) were obtained by summing the 9 GSA time points.

GH, IGF-I and ghrelin serum or plasma levels were determined and the 24-h area under the curve (AUC) and the 24-h area under the curve above the predose baseline value (AUC-BL) were calculated by trapezoidal-rule integration of the concentration-vs.-time data. A linear mixed-model analysis was carried out for AUC and for AUC-BL vs. each of the parameters. Pre-infusion and 24 h mean PP serum concentrations were determined for each patient and correlated with baseline autonomic neuropathy scores.

A descriptive exploration was made of the relationships between patient characteristics (HbA1c level, duration of diabetes mellitus, GCSI score and MNSI score) that were determined at screening and study outcomes (gastric emptying, individual and overall symptom scores). The correlation between the level of gastric emptying and symptom improvement was assessed with an exploratory analysis.

All statistical analyses and graphical outputs were generated using the open-source 'R' statistical/graphical software package, from The R Foundation for Statistical Computing, Vienna, Austria (<http://R-project.org>).

RESULTS

Thirty five patients were screened and 11 randomized to the treatment groups (Figure 1). Screen failures occurred primarily as a result of failure to meet eligibility requirements for delayed gastric emptying at both the 2 and 4 h post-meal assessment. One patient withdrew consent prior to receiving study medication. Ten patients (two in pilot; eight in definitive phase) received study medication and were included in the efficacy and safety analyses. The distribution of TZP-101 doses administered in the definitive phase was: 160 ($n = 1$), 320 ($n = 4$), and 600 ($n = 3$) $\mu\text{g}/\text{kg}$. The two patients in the pilot phase each received 80, 320 and 600 $\mu\text{g}/\text{kg}$ doses of TZP-101.

Patient demographics and baseline characteristics are shown in Table 1. Equal numbers of men and

Table 1. Demographic and baseline characteristics of enrolled patients

Characteristics	N = 10	Normal range
Age, mean years \pm s.d.	51.0 \pm 14.2	
Gender, n (%)		
Women	5 (50)	
Men	5 (50)	
Body weight, mean kg \pm s.d.	75.7 \pm 16.8	
BMI, mean kg/m ² \pm s.d.	25.3 \pm 6.3	19–25
HbA1c, mean % \pm s.d.	9.5 \pm 2.2	<7
Diabetes duration, mean years \pm s.d.	24.7 \pm 18.3	
Diabetes type, n (%)		
Type 1	7 (70)	
Type 2	3 (30)	
Michigan Neuropathy Screening Instrument (mean score* \pm s.d.)	6.2 \pm 2.5	
Autonomic neuropathy, n (%)		
Present	8 (80)	
Gastroparesis symptoms†, mean score \pm s.d.		
Average of all ratings	3.0 \pm 0.9	
Nausea/vomiting	2.2 \pm 1.3	
Postprandial fullness	3.4 \pm 1.3	
Bloating	3.3 \pm 1.9	
Gastric emptying, % retention of the radiolabelled solid meal, mean \pm s.d.		
At 2 h	61 \pm 12	
At 4 h	29 \pm 15	

* Maximum score 13.

† GCSI scale: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe for the 2 weeks preceding screening.

women with a mean age of 51.0 \pm 4.5 years and diabetes for 24.7 \pm 5.8 years were enrolled. Seven patients had type 1 diabetes. Autonomic neuropathy was present in eight patients. Mean HbA1c was 9.5 \pm 2.1% (range = 7.7–12.4) indicating less than optimal glucose control in the majority of patients. The average GCSI rating for all symptoms was 3.0 \pm 0.9. Retention of radiolabel solid meal on gastric scintigraphy was 61 \pm 12% and 29 \pm 15% at 2 and 4 h post-meal respectively. Five of the ten patients had 2 h post-meal retentions less than the 60% required by the protocol (58, 57, 57, 52, and 42). All of these patient had \geq 10% retention required at 4 h (29, 15, 10, 31 and 14) and satisfied criteria for delayed gastric emptying.²⁵

Overall, the euglycemic clamping procedure achieved the goal of maintaining blood glucose values within the target range through the post-dose gastric evaluation period.

Gastric emptying

Gastric emptying was normalized in 3/10 patients after receiving single doses of TZP-101. Normal reference values were obtained from Tougas *et al.*²⁵ and defined as 69%, 24% and 1.2% for gastric retention at 1, 2 and 4 h postmeal respectively. Half-emptying and latency times for the solid and liquid components of the meal are shown for placebo and all combined TZP-101 doses for patients in both study phases in Figure 2. The figure shows the data for all participants in the study receiving placebo (open circles, $n = 10$) and TZP-101 (closed circles, $n = 14$) and the horizontal lines indicate the mean \pm S.E.M. TZP-101 produced statistically significant reductions in gastric half-emptying (20%) ($P = 0.043$) and latency times (34%) ($P = 0.037$) for the solid meal relative to placebo. Liquid half-emptying and latency times were reduced by 28% ($P = 0.114$) and 75% ($P = 0.048$) respectively

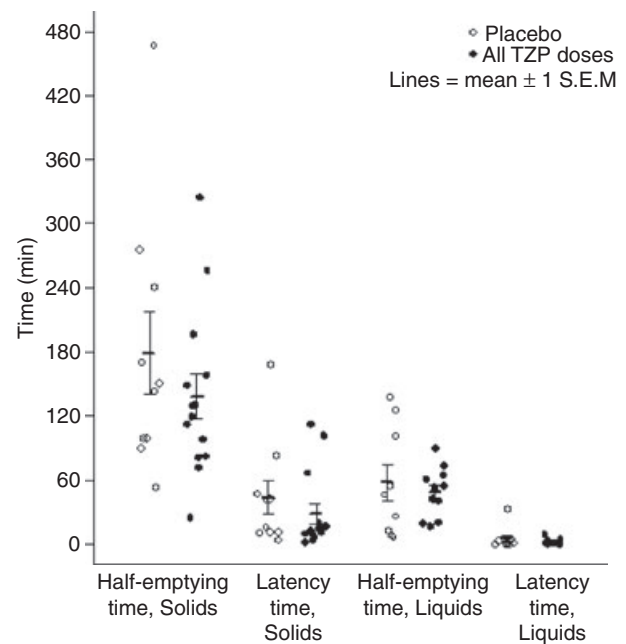


Figure 2. Solid and liquid half-emptying and latency times for all participants in the study receiving placebo (open circles, $n = 10$) and TZP-101 (closed circles, $n = 14$). Horizontal lines indicate the mean \pm S.E.M.

for all TZP-101 doses relative to placebo. There was no clear trend towards a dose response.

Symptom severity

The reduction in the mean summed GSA score of all 6 symptoms for all TZP-101 doses (12.3 ± 7.5) relative to placebo (16.1 ± 11.5) was not statistically significant ($P = 0.367$) (Figure 3). For the placebo and TZP-101 infusions respectively, scores for epigastric pain were: 0.6 ± 1.8 and 0 ± 0 , for bloating: 2.5 ± 4.4 and 2.3 ± 1.8 , for nausea: 2.8 ± 3.0 and 3.3 ± 4.0 , and for belching: 1.6 ± 2.6 and 1.4 ± 2.6 . The postprandial fullness GSA score was reduced by 37% following TZP-101 (5.4 ± 3.2 vs. 8.6 ± 4.5 after placebo) (Figure 3).

Endocrine parameters and exploratory analyses

A significant ($P = 0.047$) dose-dependent increase in GH plasma concentrations was observed in all patients while receiving TZP-101. Levels peaked at 45 min after the start of the infusion and returned to baseline levels in all but one subject by the 6-h time point. Changes in serum concentrations of IGF-I and ghrelin over time were not conclusive and the slopes of the 24 h AUC and AUC-BL for these factors were not significantly different from zero.

Autonomic neuropathy correlated negatively with the level of PP at baseline ($r = -0.732$, $P = 0.062$) and for 24 h after TZP-101 infusions ($r = -0.772$,

$P = 0.025$) such that patients with more severe neuropathy had lower levels of PP.

An exploratory analysis of the correlations between baseline symptoms and efficacy outcomes showed a trend for high baseline GCSI scores and low MNSI scores to be associated with better improvements in gastric-emptying parameters. There were no clear associations between HbA1c and duration of diabetes with gastric-emptying parameters or between any of the baseline characteristics and symptom severity scores. There was no correlation between the degree of autonomic neuropathy or levels of PP at baseline and improvement in gastric emptying ($r = 0.205$, $P = 0.660$ for PP).

No correlation was revealed between improvement in overall GSA score and reductions in the gastric emptying parameters as assessed in the exploratory analysis.

Tolerability

The two patients in the pilot phase experienced 21 adverse events: 7 following placebo, and 4, 6 and 4 following the 80, 320 and 600 $\mu\text{g}/\text{kg}$ TZP-101 doses respectively. Orthostatic hypotension was observed one time each following placebo, 80 $\mu\text{g}/\text{kg}$ and 320 $\mu\text{g}/\text{kg}$ dosing. Thirty-one adverse events occurred in the 8 patients in the definitive phase: 12 following placebo, and 1, 3, and 15 following the 160, 320 and 600 $\mu\text{g}/\text{kg}$ TZP-101 doses respectively. One patient in the 600 $\mu\text{g}/\text{kg}$ group had 10 events of panic not attributed to study medication. Most adverse events were mild and self-limiting and there were no identifiable differences in numbers or types of adverse events between TZP-101 and placebo. Three treatment-emergent serious adverse events occurred in three patients, none of which was considered related to study treatment: haematemesis resulting in hospitalization following placebo infusion, skin ulceration following placebo infusion, and vomiting following 320 $\mu\text{g}/\text{kg}$ TZP-101 infusion. One patient had a temporary decrease in heart rate 45 min after starting the 600 $\mu\text{g}/\text{kg}$ infusion. No clinically or statistically significant changes in vital signs or ECG parameters were found following TZP-101 infusions compared to placebo.

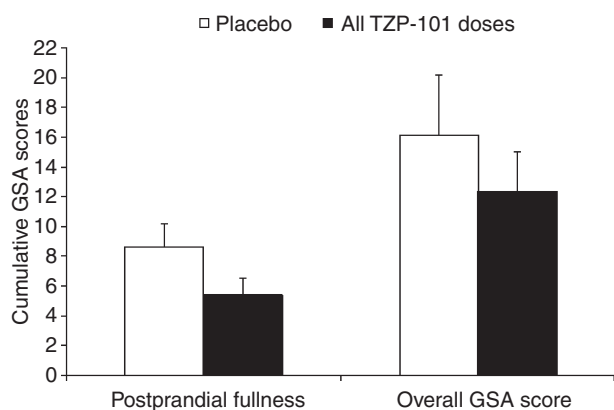


Figure 3. Cumulative GSA scores (mean \pm S.E.M.) for postprandial fullness ($P = 0.142$) and overall ($P = 0.367$) after receiving placebo and all TZP-101 doses. Higher scores indicate greater severity of symptoms.

DISCUSSION

This study demonstrated that a single dose of TZP-101 improves solid-meal gastric half-emptying and

solid- as well as liquid-meal latency time in diabetes patients with gastroparesis. Gastric emptying of the solid meal was normalized in a third (3/10) of patients after a single TZP-101 infusion. Due to the small number of patients in each dose group, a meaningful conclusion regarding dose effects could not be made in the present study and comparisons were made between placebo and all dose groups combined. The improvements in gastric emptying after TZP-101 infusion are similar in magnitude to those observed in diabetes patients with gastroparesis following ghrelin infusions.^{13, 15}

Patients' baseline severity rating for postprandial fullness was the highest of the gastrointestinal symptoms assessed. Postprandial fullness has been described as the primary upper gastrointestinal symptom associated with delayed gastric emptying in patients with both idiopathic and diabetes-related gastroparesis.^{26, 27} TZP-101 infusion resulted in a 37% decrease in severity of postprandial fullness relative to placebo that is comparable to the 29% decrease in severity of postprandial fullness rated by patients with idiopathic gastroparesis following ghrelin infusion.¹⁴

While the overall severity of gastrointestinal symptoms decreased following TZP-101 dosing compared to placebo, the changes were not statistically significant. The sample size was calculated for the endpoint of gastric emptying, but not for changes in gastrointestinal symptoms. The lack of statistical significance with regard to gastrointestinal severity scores may be attributable to the relatively small sample size and, therefore, does not preclude an effect of TZP-101. However, lack of correlation between improvements in gastric emptying and upper gastrointestinal symptoms in diabetes patients has been previously described. Murray *et al.*¹³ demonstrated that ghrelin improved gastric emptying rates in diabetes patients with gastroparesis without significant effects on patient assessment of bloating or nausea. Similarly, nausea and bloating were not improved in patients with idiopathic gastroparesis following ghrelin infusion.¹⁴ The small number of patients in these exploratory studies prevents conclusions regarding GHSR agonist effects on gastroparesis symptom severity.

We also explored the relationship between baseline symptoms and efficacy outcomes and showed a trend for more severe symptoms and neuropathy to be associated with greater improvements in gastric emptying outcomes following TZP-101 infusion. These data suggest that diabetes patients with moderate-to-severe

gastroparesis may benefit from TZP-101. As no currently available drug efficiently accelerates gastric emptying, there is an unmet need for effective treatment of patients with gastroparesis and poor metabolic control to avoid co-morbidities or progression to surgery.

The clinical characteristics of this small patient population were studied in detail. The patient population displayed, in addition to neuropathy, poor glycemic control evidenced by high baseline HbA1c. A hyperinsulinemic-euglycemic clamp procedure was used to stabilize blood glucose levels prior to and up to 4 h after every infusion. As acute post-prandial changes in blood glucose concentration can significantly alter upper-gut motor and sensory function,²⁸ use of the euglycemic clamp is essential in studies evaluating gastroduodenal drugs. Overall, glucose levels were held within the target range. Therefore, the observed significant improvements in gastric emptying were independent of glucose levels and can be attributed to effects of TZP-101.

There were no safety concerns that arose during the study. Special attention was paid to monitoring changes in cardiac parameters due to previous healthy volunteer data demonstrating that 600 µg/kg briefly decreased heart rate.¹⁷ There were no clinically relevant changes in cardiac parameters. A majority of patients in the current study had signs of autonomic neuropathy that may have played a role in the lack of TZP-101 effects on heart rate. Consistent with altered autonomic function was the finding that secretion of PP before a meal and after a meal inversely correlated with severity of neuropathy.²⁹

Despite the presence of vagal impairment in these diabetes patients, TZP-101 significantly improved gastric emptying, suggesting that mechanisms in addition to vagal afferent pathways mediate ghrelin action in the gastrointestinal tract. Similarly, ghrelin infusion following a solid meal induced a greater than 30% reduction in the half-emptying time in patients with gastroparesis attributed to vagal dysregulation (diabetes and surgical vagotomy).¹⁵ This suggests that gastroduodenal action of the ghrelin pathway can be mediated via extravagal mechanisms. *In vitro* and *in vivo* studies have identified ghrelin receptors on myenteric, vagal and central neurons indicating that ghrelin may affect gastrointestinal motility via multiple neural signalling pathways (reviewed in³⁰).

As the ghrelin pathway positively regulates both GH and IGF-I and ghrelin increases GH in diabetes

patients with gastroparesis,¹³ we examined whether TZP-101 infusion altered concentrations of GH or IGF-I. The effects of TZP-101 on serum levels of IGF-I were inconclusive. However, consistent increases in serum GH were seen with all TZP-101 doses. Similar results were reported in healthy volunteers who received TZP-101 infusions.¹⁷ It is not anticipated that the expected, transient changes in GH following TZP-101 or ghrelin infusions^{13, 15} will have health consequences.

In summary, this proof-of-concept study demonstrates that the ghrelin receptor agonist TZP-101 is well tolerated in diabetes patients with moderate-to-severe gastroparesis and shows statistically significant improvement in gastric emptying. Future studies should be performed to investigate the long-term effects of ghrelin agonists on gastroparesis and glycaemic control in this seriously diseased group of diabetes patients.

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REFERENCES

- Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum R. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term followup of patients with gastroparesis. *Dig Dis Sci* 1998; **43**: 2398–404.
- Talley NJ, Young L, Bytzer P, *et al.* Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. *Am J Gastroenterol* 2001; **96**: 71–6.
- Horowitz M, O'Donovan D, Jones KL, Feinle C, Rayner CK, Samsom M. Gastric emptying in diabetes: clinical significance and treatment. *Diabet Med* 2002; **19**: 177–94.
- Kuo P, Rayner CK, Jones KL, Horowitz M. Pathophysiology and management of diabetic gastropathy: a guide for endocrinologists. *Drugs* 2007; **67**: 1671–87.
- Friedenberg FK, Parkman HP. Advances in the management of gastroparesis. *Curr Treat Options Gastroenterol*. 2007; **10**: 283–93.
- Abell TL, Bernstein RK, Cutts T, *et al.* Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006; **18**: 263–83.
- Ejksjaer NT, Bradley JL, Buxton-Thomas MS, *et al.* Novel surgical treatment and gastric pathology in diabetic gastroparesis. *Diabet Med* 1999; **16**: 488–95.
- Guy RJ, Dawson JL, Garrett JR, *et al.* Diabetic gastroparesis from autonomic neuropathy: surgical considerations and changes in vagus nerve morphology. *J Neurol Neurosurg Psychiatry* 1984; **47**: 686–91.
- Watkins PJ, Buxton-Thomas MS, Howard ER. Long-term outcome after gastrectomy for intractable diabetic gastroparesis. *Diabet Med* 2003; **20**: 58–63.

- 10 Jones MP, Maganti K. A systematic review of surgical therapy for gastroparesis. *Am J Gastroenterol* 2003; **98**: 2122–9.
- 11 Date Y, Kojima M, Hosoda H, *et al.* Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 2000; **141**: 4255–61.
- 12 Fukuda H, Mizuta Y, Isomoto H, *et al.* Ghrelin enhances gastric motility through direct stimulation of intrinsic neural pathways and capsaicin-sensitive afferent neurones in rats. *Scand J Gastroenterol* 2004; **39**: 1209–14.
- 13 Murray CD, Martin NM, Patterson M, *et al.* Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. *Gut* 2005; **54**: 1693–8.
- 14 Tack J, Depoortere I, Bisschops R, Verbeke K, Janssens J, Peeters T. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. *Aliment Pharmacol Ther* 2005; **22**: 847–53.
- 15 Binn M, Albert C, Gougeon A, *et al.* Ghrelin gastrokinetic action in patients with neurogenic gastroparesis. *Peptides*. 2006; **27**: 1603–6.
- 16 Vestergaard ET, Hansen TK, Gormsen LC, *et al.* Constant intravenous ghrelin infusion in healthy young men: clinical pharmacokinetics and metabolic effects. *Am J Physiol Endocrinol Metab*. 2007; **292**: E1829–36.
- 17 Lasseter KC, Shaughnessy L, Cummings D, *et al.* Ghrelin agonist (TZP-101): safety, pharmacokinetics and pharmacodynamic evaluation in healthy volunteers: a phase I, first-in-human study. *J Clin Pharmacol* 2008; **48**: 193–202.
- 18 Venkova K, Fraser G, Hoveyda HR, Greenwood-Van Meerveld B. Prokinetic effects of a new ghrelin receptor agonist TZP-101 in a rat model of postoperative ileus. *Dig Dis Sci* 2007; **52**: 2241–8.
- 19 Revicki DA, Rentz AM, Dubois D, *et al.* Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. *Qual Life Res* 2004; **13**: 833–44.
- 20 Feldman EL, Stevens MJ. Clinical testing in diabetic peripheral neuropathy. *Can J Neurol Sci* 1994; **21**: S3–7.
- 21 Rosenfalck AM, Almdal T, Viggers L, Madsbad S, Hilsted J. A low-fat diet improves peripheral insulin sensitivity in patients with Type 1 diabetes. *Diabet Med* 2006; **23**: 384–92.
- 22 Guo JP, Maurer AH, Fisher RS, Parkman HP. Extending gastric emptying scintigraphy from two to four hours detects more patients with gastroparesis. *Dig Dis Sci* 2001; **46**: 24–9.
- 23 Espelund U, Hansen TK, Hojlund K, *et al.* Fasting unmasks a strong inverse association between ghrelin and cortisol in serum: studies in obese and normal-weight subjects. *J Clin Endocrinol Metab* 2005; **90**: 741–6.
- 24 Tougas G, Chen Y, Coates G, *et al.* Standardization of a simplified scintigraphic methodology for the assessment of gastric emptying in a multicenter setting. *Am J Gastroenterol* 2000; **95**: 78–86.
- 25 Tougas G, Eaker EY, Abell TL, *et al.* Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol* 2000; **95**: 1456–62.
- 26 Jones KL, Russo A, Stevens JE, Wishart JM, Berry MK, Horowitz M. Predictors of delayed gastric emptying in diabetes. *Diabetes Care* 2001; **24**: 1264–9.
- 27 Stanghellini V, Tosetti C, Horowitz M, *et al.* Predictors of gastroparesis in outpatients with secondary and idiopathic upper gastrointestinal symptoms. *Dig Liver Dis*. 2003; **35**: 389–96.
- 28 Rayner CK, Samsom M, Jones KL, Horowitz M. Relationships of upper gastrointestinal motor and sensory function with glycemic control. *Diabetes Care* 2001; **24**: 371–81.
- 29 Chey WY, Chang T. Neural hormonal regulation of exocrine pancreatic secretion. *Pancreatol* 2001; **1**: 320–35.
- 30 Peeters TL. Central and peripheral mechanisms by which ghrelin regulates gut motility. *J Physiol Pharmacol* 2003; **54**(Suppl 4): 95–103.