

Ghrelin Agonist (TZP-101) Effects on Severe Symptomatic Diabetic Gastroparesis

Niels Ejskjaer MD PhD
Department of Medicine
Aarhus University Hospital
Denmark

Presenter Disclosure Information

Niels Ejksjaer MD PhD

Aarhus University Hospital, Denmark

Research Support: Tranzyme Pharma

Advisory Panel: Eli Lilly, Medicus

Engineering, Medtronic, Novo Nordisk,
Pfizer, Tranzyme Pharma



Background

- ◆ Definition Diabetic Gastroparesis:
Non-obstructive impairment of gastric propulsive activity
- ◆ Symptoms:
 - postprandial fullness, nausea, vomiting, bloating, early satiety and epigastric pain
- ◆ Pathophysiology:
 - Autonomic (vagal) neuropathy - Intrinsic neuropathy
 - Acute elevations of blood glucose
 - Psychosomatic factors
- ◆ Escalating prevalence of disorder
- ◆ Minimal treatment options available
- ◆ Search for new treatments

Ghrelin

- ◆ 28 amino acid peptide
- ◆ Predominantly present in gastric endocrine cells
- ◆ Contributes to regulation of diverse functions of gut-brain axis

Ghrelin Role in Diabetic Gastroparesis

- ◆ Reduced density of ghrelin-immunoreactive cells in animal models of human type 1 & 2 diabetes (*Rauma, 2006*)
- ◆ Induces migrating motor complex in humans (*Tack, 2005*)
- ◆ Accelerates gastric emptying in humans (*Binn 2006, Levin 2007, Murray 2005, Tack 2006*)

TZP-101 Ghrelin Agonist

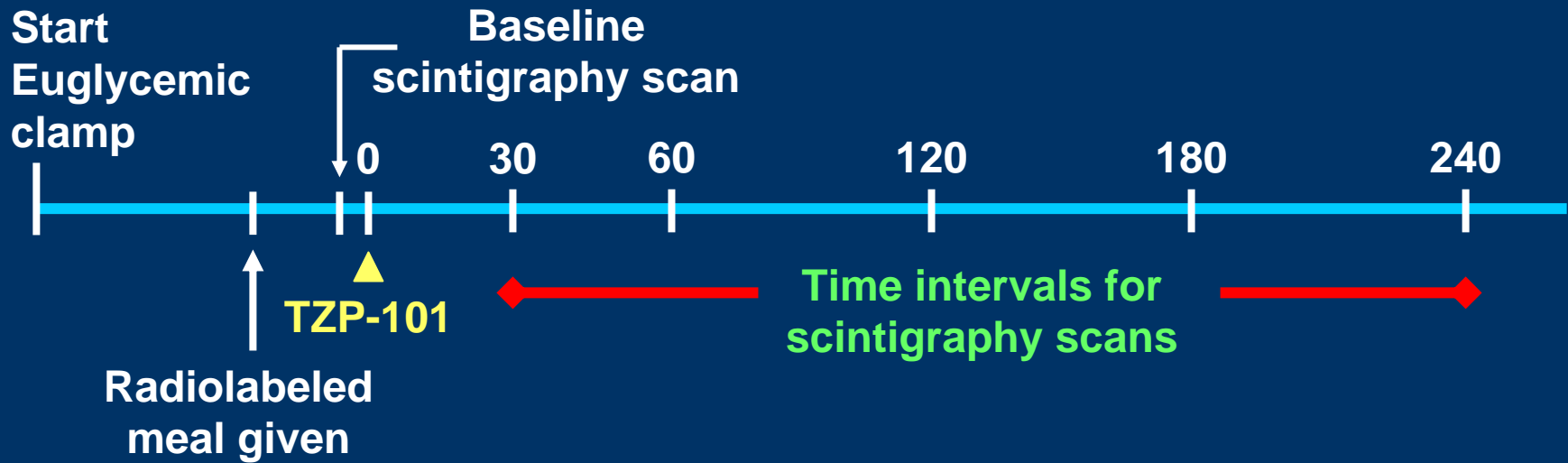
- ◆ Agonist at the cloned human ghrelin receptor
 - ▶ Highly potent, reversible, selective
- ◆ Restores gastroprokinetic activity (animal models) impaired by:
 - ▶ Surgical manipulation; morphine; surgery + morphine
 - ▶ High caloric meal (gastroparesis)
- ◆ 50 healthy subjects data suggests:
 - ▶ Good tolerability and safety profile @ doses 20-600 μ g/kg
 - ▶ Pharmacokinetics that allow single daily administration
 - ▶ Activity at receptor level of doses as low as 20 μ g/kg

Proof of Principle Study

◆ Objectives

- ▶ To evaluate TZP-101 prokinetic properties in patients with delayed gastric emptying
 - Primary endpoint: Half-emptying time of radio-labelled solid meal

Proof of Principle Study Design



- ◆ Diabetic patients with symptoms of gastroparesis plus delayed gastric emptying (retention >60% at 2 hours; >10% at 4 hours)
 - ▶ TZP-101: 30 min iv infusion of 80-600 μ g/kg vs. placebo (two-way, cross-over)
 - ▶ Glucose clamped at 6-8mmol/L
 - ▶ Scintigraphy at 0, 0.5, 1, 2, 3, and 4 hour
 - ▶ Symptoms assessed every 30 minutes for 4 hours (GSA)

Procedures & Methods

- ◆ Hyperinsulinemic / euglycemic clamp (*De Fronzo, 1979*)
- ◆ Scintigraphy performed after 99mTc-labeled egg sandwich meal (two scrambled eggs, two pieces of toasted bread; 282 kcal) and 300 ml 111In- DTPA-labeled water (*Guo, 2001*)

Statistics

- ◆ 10 patients - to provide 80% power to detect treatment effect for any gastric-emptying endpoint
- ◆ Half emptying and latency times were obtained from regression analysis of gastric emptying data using a “power-exponential” model (*Tougas, 2000*)
- ◆ Cumulative GSA Scores (overall and individual symptom) were obtained by summing the 9 GSA time points

Study Results

- ◆ Demographics & Baseline Characteristics
- ◆ Safety
- ◆ Endocrine Response
- ◆ Gastric Emptying
- ◆ Symptom Improvement

Demographics & Baseline Characteristics

- ◆ 10 diabetic patients
 - ▶ 7 type 1; 3 type 2
 - ▶ 5F/5M; 51 (24-68) years of age
 - ▶ 25 years (6-57) duration of diabetes
 - ▶ 9.5% (7.2-13) HbA1c
- ◆ Gastroparesis Cardinal Symptom Index (GCSI)
 - ▶ Average: 2.95 (1.81-4.47)
- ◆ Gastric emptying data
 - ▶ 61 (42-84)% at 2 hours; 29 (10-50)% at 4 hours

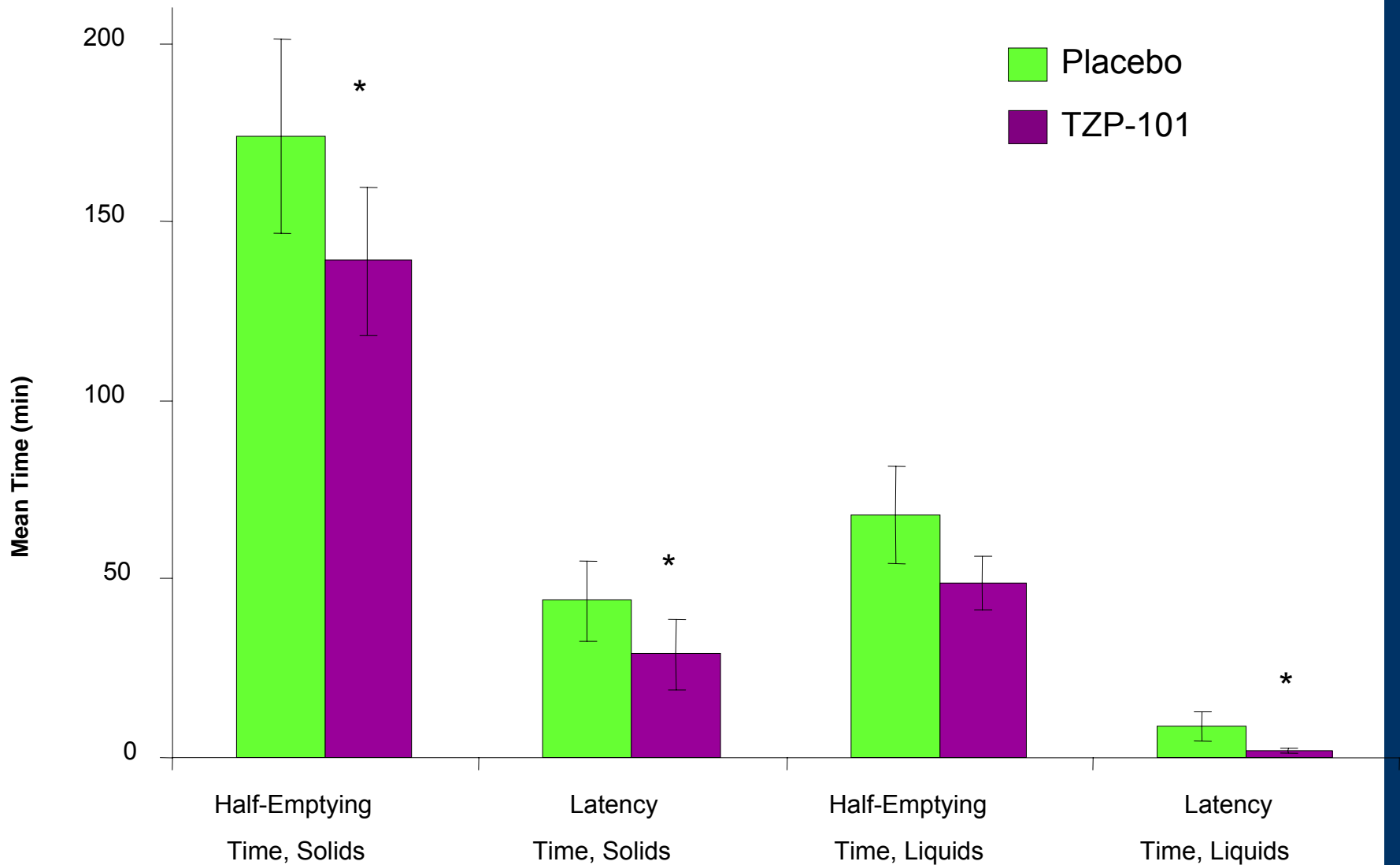
Safety; Endocrine Response

- ◆ Safe and well-tolerated
- ◆ The observed endocrine response suggested activity at the receptor level
 - ▶ Serum Growth Hormone levels temporarily elevated

Gastric Emptying Response

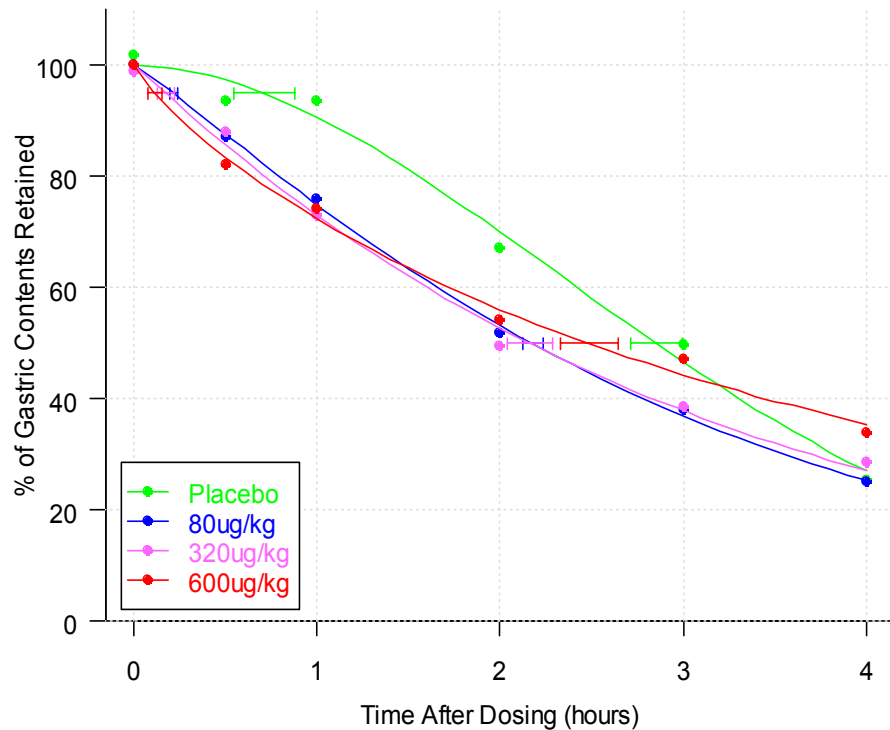
- ◆ TZIP-101 accelerated gastric emptying of solid radiolabeled meal in 8/10 patients
 - ▶ Significant reduction in half-emptying time for solid meal ($p=0.043$)
 - ▶ Gastric emptying was normalized in three patients
- ◆ The response did not appear to be dose-related

Gastric Emptying Response: Solid and Liquid Meal Half Emptying and Latency Times (mean \pm SEM) * $p < 0.05$ compared with placebo

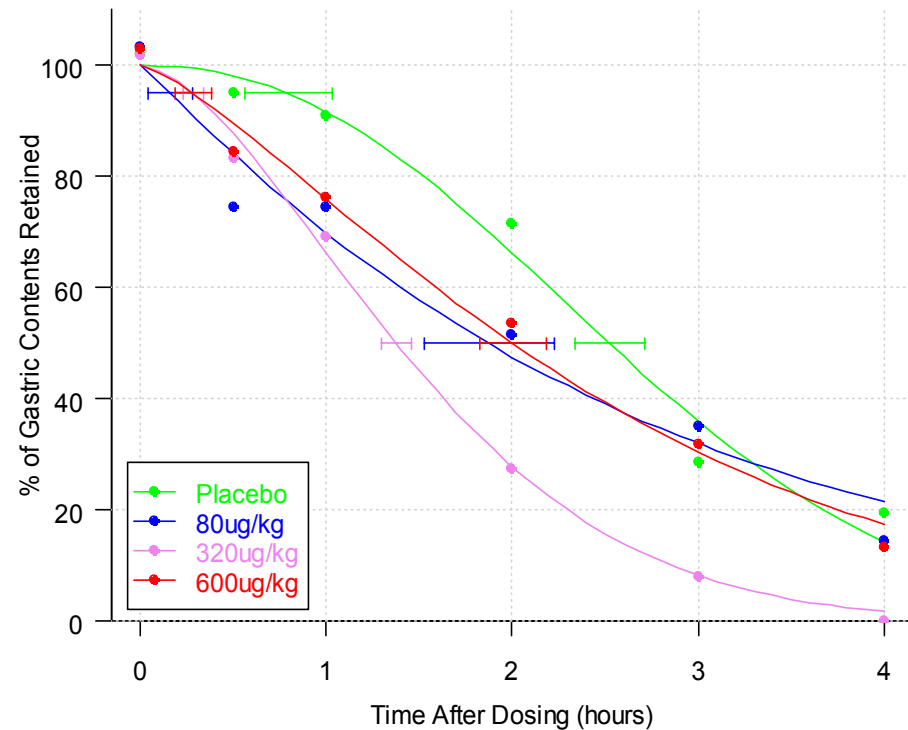


Gastric Emptying: Data from two patients that had received 3 TZP-101 doses and placebo

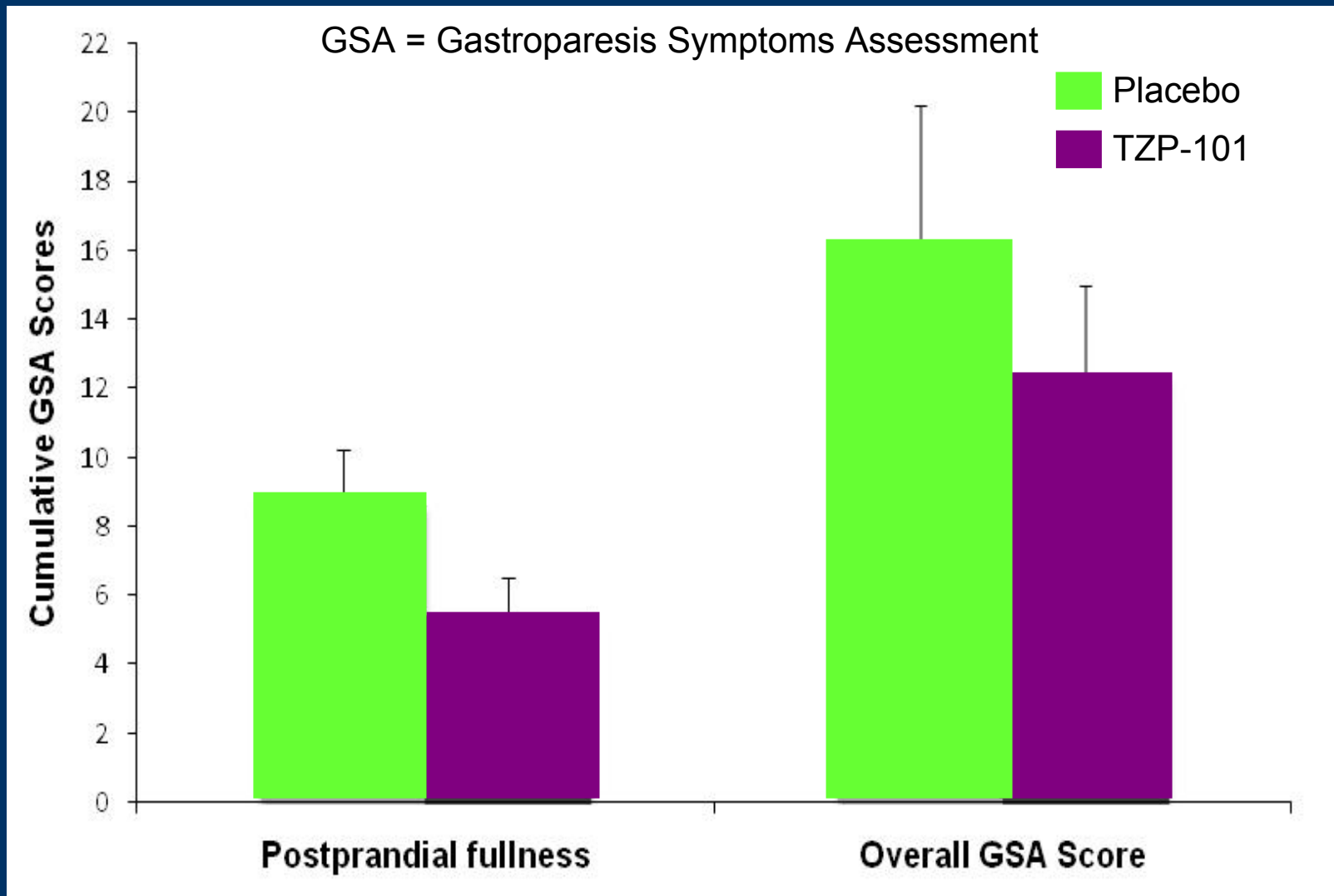
Gastric Emptying Analysis for Subject = 903



Gastric Emptying Analysis for Subject = 904



Symptom Improvement: Cumulative GSA Scores for Overall and Postprandial Fullness (mean \pm SEM)



Discussion

- ◆ Observed gastric emptying improvement is consistent with published data on ghrelin administration to humans (*Tack, Murray*)
- ◆ A 37% decrease in severity of postprandial fullness is of special importance as
 - ▶ this symptom has been described as the primary upper gastrointestinal symptom associated with delayed gastric emptying in patients with both idiopathic and diabetes-related gastroparesis (Jones, 2001; Stanghellini, 2003)

Conclusions

- ◆ **Single-dose** TZP-101 statistically superior to placebo in diabetic patients with symptomatic gastroparesis
 - ▶ Significant improvement of gastric emptying
 - ▶ Emptying normalized in 3 of 10 subjects
 - ▶ Trend toward symptom improvements

Data mandates need for further clinical evaluation of TZP-101