Pharmacodynamic Effects of Ghrelin Agonist Relamorelin (RM-131) in Patients with Type 1 and Type 2 Diabetes Mellitus and Delayed Gastric Emptying

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Disclosures

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Outline

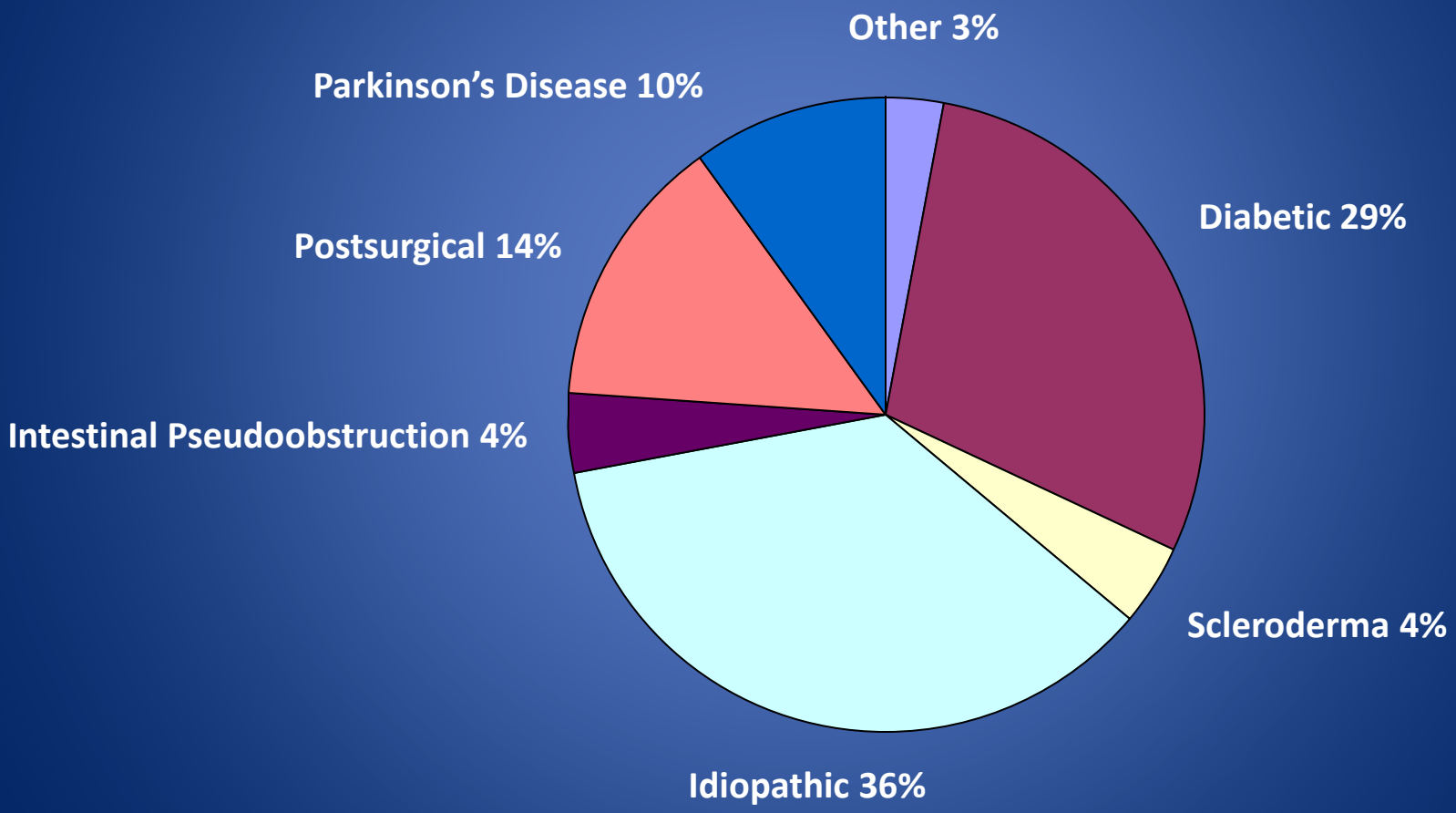
- Background
  - Clinical Symptoms
  - Diagnostic Assessment
  - Pharmacologic Therapies
- Aims
- Findings and Results
- Summary and Future Directions

Diabetic Gastroparesis

- Upper GI symptoms and delayed gastric emptying (GE)
  - Nausea, vomiting, early satiety (fullness), bloating, pain
  - Asymptomatic (delayed GE)
- Symptoms in 5-12% patients with diabetes[1,2]
  - Poorer glycemic control
  - Anxiety, depression, and neuroticism[3]
- More likely to have cardiovascular disease, nephropathy, hypertension, retinopathy[4]

1. Bytzer P et al. Arch Intern Med 2001
2. Maleki D et al. Arch Intern Med 2000
3. Talley NJ et al. Am J Gastroenterol 2001
4. Hyett B et al. Gastroenterology 2009

Diabetic Gastroparesis is a common cause of gastroparesis among tertiary referral patients



Bityutskiy et al. Am J Gastroenterol 1997

Comparison of techniques for GE assessment

	Scintigraphy	Stable isotope breath test	Wireless pressure and pH capsule	Ultrasonography
Indication / function measured	Gastric emptying	Gastric emptying	Emptying and pressure amplitude	Gastric emptying
Device, assembly or special requirements	External gamma camera; isotope-labeled meal	Breath collection vials; stable isotope-labeled meal	Intraluminal capsule with miniaturized strain gauge and pH measurement	2D or 3D ultrasound equipment
Placement of device	-	-	Capsule swallowed	On abdomen repeatedly
Performance / versatility / interpretation	Excellent; standardized meals, data acquisition and interpretation	Becoming standardized; performance related to mathematics analysis	Standard acquisition; delayed emptying fairly valid; pressures of unclear significance	Becoming standardized; performance related to technical expertise; best for liquid emptying
Duration of study (hours, h)	Typically 4h, could be added to small bowel and colon transit	3-4h	6h, could be added to small bowel and colon transit	Typically 2h
Availability / potential use	+	+++	+	+
Cost	++	+	++	++

Szarka LA, Camilleri M. Am J Physiol 2009

Gastric Emptying Scintigraphy (GES)

- Gold standard for GE assessment
  - Society of Nuclear Medicine & The American Neurogastroenterology and Motility Society
- Performed with standard low-fat meal
- Solid-phase GE to document delayed GE
- Simultaneous assessment of liquid GE
  - May ↑ sensitivity?
  - Relationship between solid and liquid GE unclear

Indications for GES

- Diabetic patients with upper GI symptoms
- Poor glycemic control
- Considering or are taking hypoglycemic medications that may slow GE
- Severe reflux symptoms

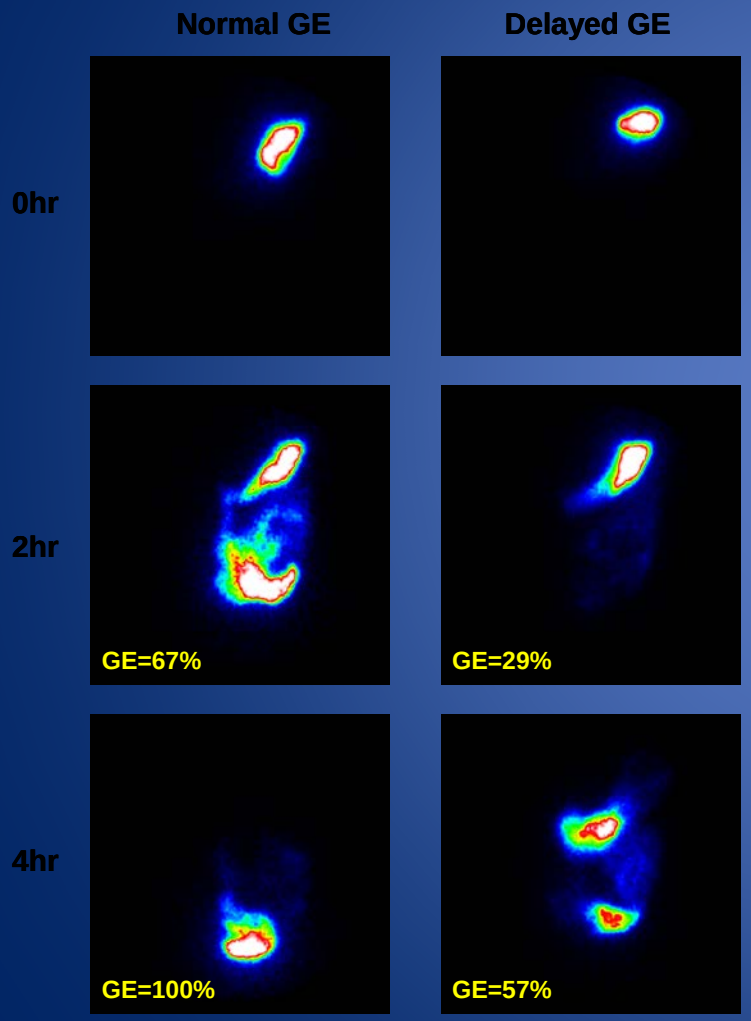
GES Preparation

- Stop all motility-altering medications for 2-3 days (prokinetics, opiates, anticholinergics)
- No smoking/alcohol consumption on test day
- Fasting blood glucose < 275 mg/dL on test day**
  - What level of hyperglycemia is important?
    - Bytzer et al. Am J Gastroenterol 2002
    - Bharucha et al. Clin Endocrinol (Oxf). 2009
    - Hasler WL et al. Gastro 1995
    - Bharucha et al. Clin Gastroenterol Hepatol 2014

GES Procedure

- Procedure:
  - Overnight fast
  - Standardized test meal within *10 minutes* (255kcal)
  - Imaging at baseline, 1, 2, 4 hours after meal ingestion
  - Minimum of 4 hours for reliable estimate of $T_{1/2}$

Normal and delayed GE in patient with type 1 DM



- Quantification of GE using computerized software
- Results are expressed as % radioactivity retained in the stomach at each time point
- Delayed GE if:
  - > 60% retention at 2h or
  - > 10% retention at 4 hours
- Females on average 15% slower than males

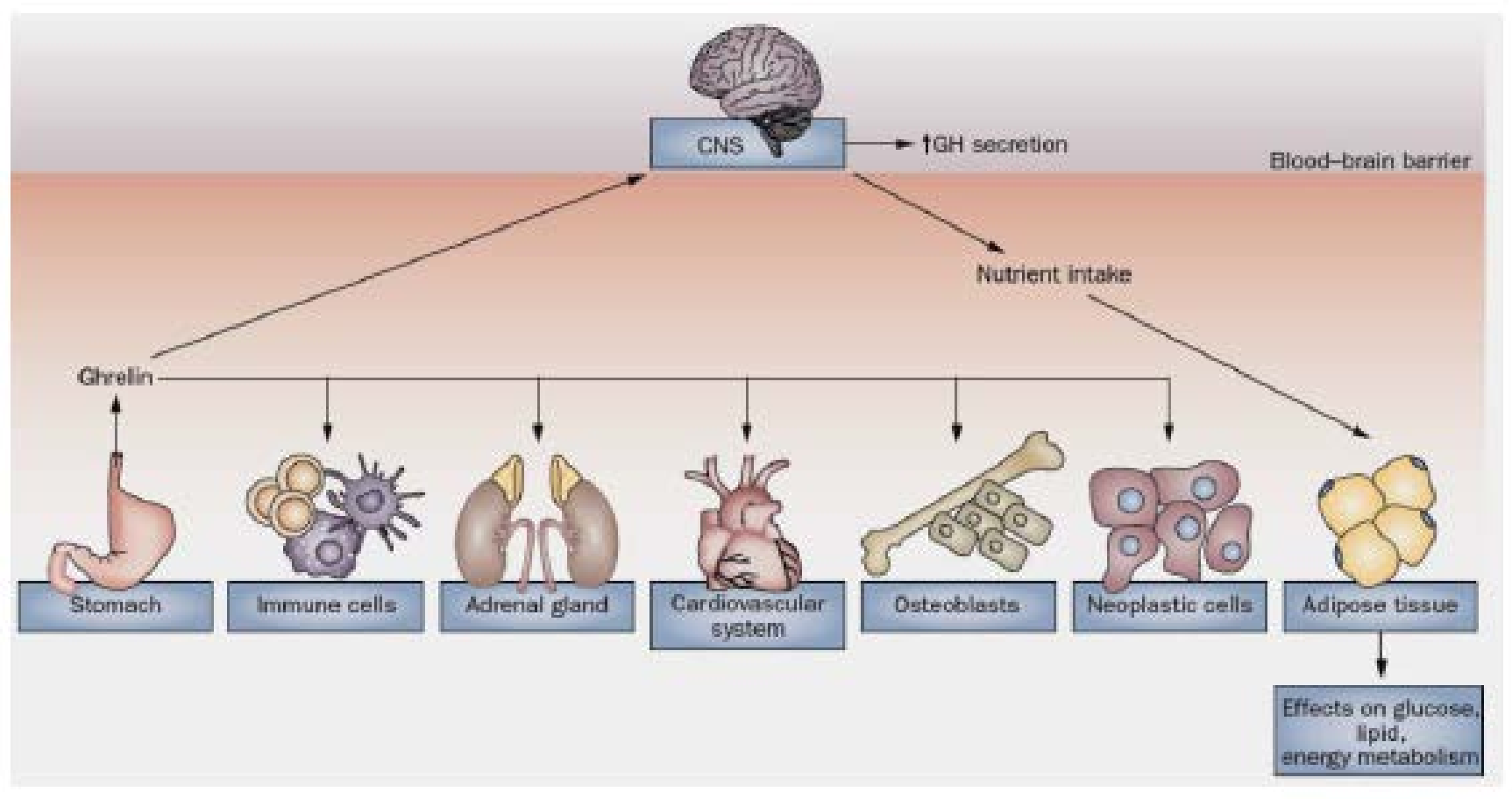
Merits & Limitations of GES

★★★	✖✖✖
Non-invasive	Radiation exposure
Direct measure of GE	Limited access to gamma-camera
Quantitative assessment	Lack of adherence to standardized protocol
Assess GE both solids and liquids	Significant intra-individual CV (24%)?
Characterize intragastric distribution of contents	Limitations of low-fat, low-fiber meal

Treatment for Gastroparesis

- First line therapy:
  - Nutrition, hydration, glycemic control
- Metoclopramide
  - Risk of neurological side effects (tardive dyskinesia)
  - Limited to no more than 3 consecutive months
- Domperidone
- Erythromycin
  - tachyphylaxis
- Symptomatic treatment
  - anti-emetics, pain management
- Surgery and/or Botox

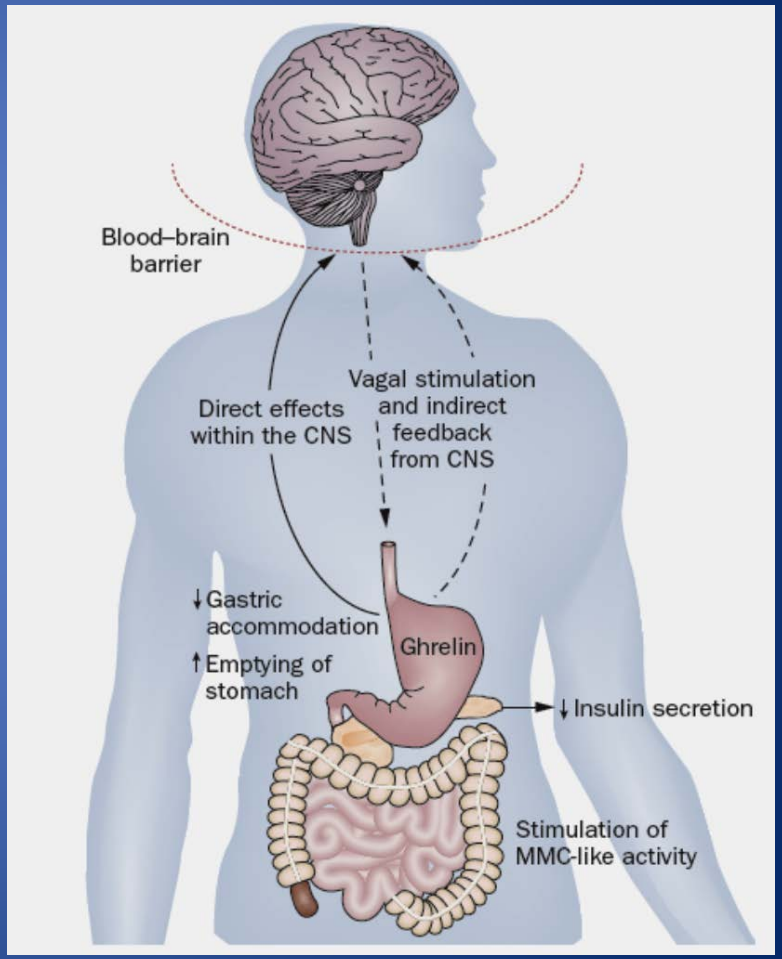
Ghrelin



Camilleri M et al. Nat Rev Gastroenterol Hepatol 2009

The role of Ghrelin

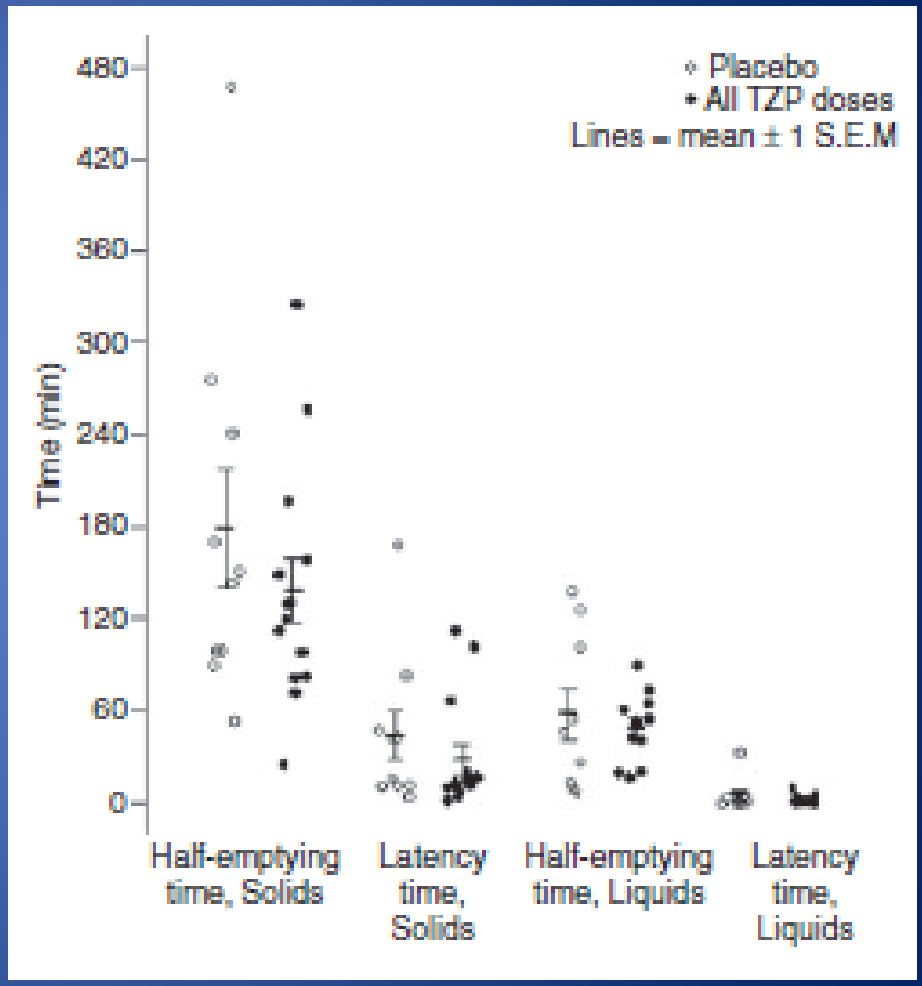
- Promotes gastric motility in animal models
- Ghrelin is a potential treatment for delayed gastric emptying (DGE)
- Short half-life, plasma instability



Camilleri M et al. Nat Rev Gastroenterol Hepatol 2009

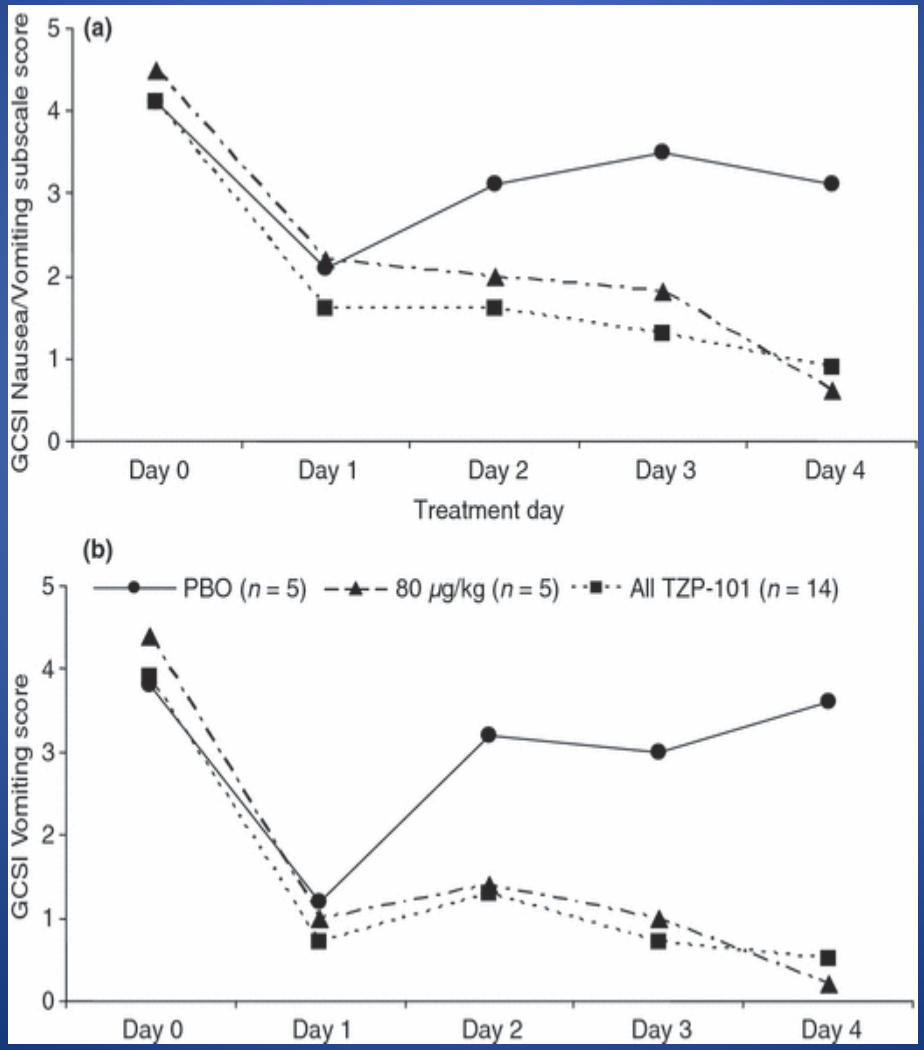
Synthetic Ghrelin Agonists

- TZP-101 (ulimorelin)
  - Macrocyclic peptidomimetic
  - Potent binding affinity for the ghrelin receptor
  - Accelerated GE



Ejskaer N et al. Aliment Pharmacol Ther 2009

Change in mean Nausea/Vomiting subscale scores (a) and Vomiting scores (b) over time.



Wo et al. Aliment Pharmacol Ther 2010

A phase 2a, DB, RCT 28-day study of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis

- **Background**: TZP-102 (macrocyclic, selective, oral ghrelin-R agonist)
- **Methods** DB, RCT of 92 outpatients with diabetic gastroparesis; once-daily 10-mg (*n* = 22), 20-mg (*n* = 21), 40-mg (*n* = 23) TZP-102 or placebo (*n* = 26). The primary endpoint was the change in GE $T_{½}$ utilizing ^{13}C-Octanoate breath test (350 kcal, 7g fat meal)

	10 mg TZP-102	20 mg TZP-102	40 mg TZP-102	All TZP-102	Placebo
Baseline (Day −16 to −7)					
N	13	13	15	41	15
Mean (SD)	216.9 (66.7)	215.6 (55.3)	207.4 (36.9)	213.0 (52.4)	224.1 (57.4)
Day 28					
N	13	13	15	41	15
Mean (SD)	197.2 (54.8)	186.4 (65.6)	170.2 (30.5)	183.9 (51.5)	179.9 (55.6)
Day 28 CFB					
N	13	13	15	41	15
Mean (SD)	−19.7 (57.2)	−29.2 (48.1)	−37.2 (36.98)	−29.1 (46.97)	−44.2 (46.0)
P-value (*vs* Placebo)	0.325	0.639	0.864	0.606	

- **Conclusion**: TZP-102 for 28 days, at doses of 10-40mg once daily, does not accelerate gastric emptying but it is was well-tolerated and resulted in a reduction in symptoms of gastroparesis

Ejskaer N et al. Neurogastroenterol Motil 2013

Oral TZP-102 in Diabetic Gastroparesis

- **Aim:** Two phase 2b RCTs (TZP-102-CL-G003 and TZP-102-CL-G004) to evaluate 12 weeks of oral TZP-102 in patients with diabetic gastroparesis
- **Primary outcome**: Average change from baseline through end-of treatment in Daily Diary of Gastroparesis Symptoms Questionnaire (GSDD)
- **Results**: Improvement in the GSDD observed in all treatment arms

	10 mg TZP-102	10 mg TZP-102	10 mg TZP-102	20 mg TZP-102	20 mg TZP-102	20 mg TZP-102	Placebo	Placebo	Placebo
	BL	Week 12	Δ from BL	BL	Week 12	Δ from BL	Baseline	Week 12	Δ from BL
GSDD Composite score	3.5±0.6	1.8±1.2	-1.7±1.2 P=0.07	3.7±0.6	2.2±1.3	-1.4±1.3 P=0.68	3.6±0.6	2.1±1.1	-1.5±1.2

McCallum RW et al. Neurogastroenterol Motil 2013

Novel ghrelin agonist, RM-131

- RM-131 (Relamorelin)
  - Pentapeptide synthetic ghrelin agonist
  - Longer plasma $T_{1/2}$
  - >100-fold potency for prokinetic effects than native ghrelin in animal models
  - PK and PD data from healthy volunteer studies
    - Single-ascending dose study of 36 healthy males
    - Mean $T_{1/2}$ for elimination 5-19 hours
    - Acceleration of GE at doses ≥ 10 µg
    - Maximal effect at 100 µg dose level

Randomized Controlled Phase Ib Study of Ghrelin Agonist, RM-131, in Type 2 Diabetic Women with Delayed Gastric Emptying: Pharmacokinetics and Pharmacodynamics

Shin A, Camilleri M, Busciglio I, Burton D, Stoner E, Noonan P, Gottesdiener K, Smith SA, Vella A, Zinsmeister AR

Objectives

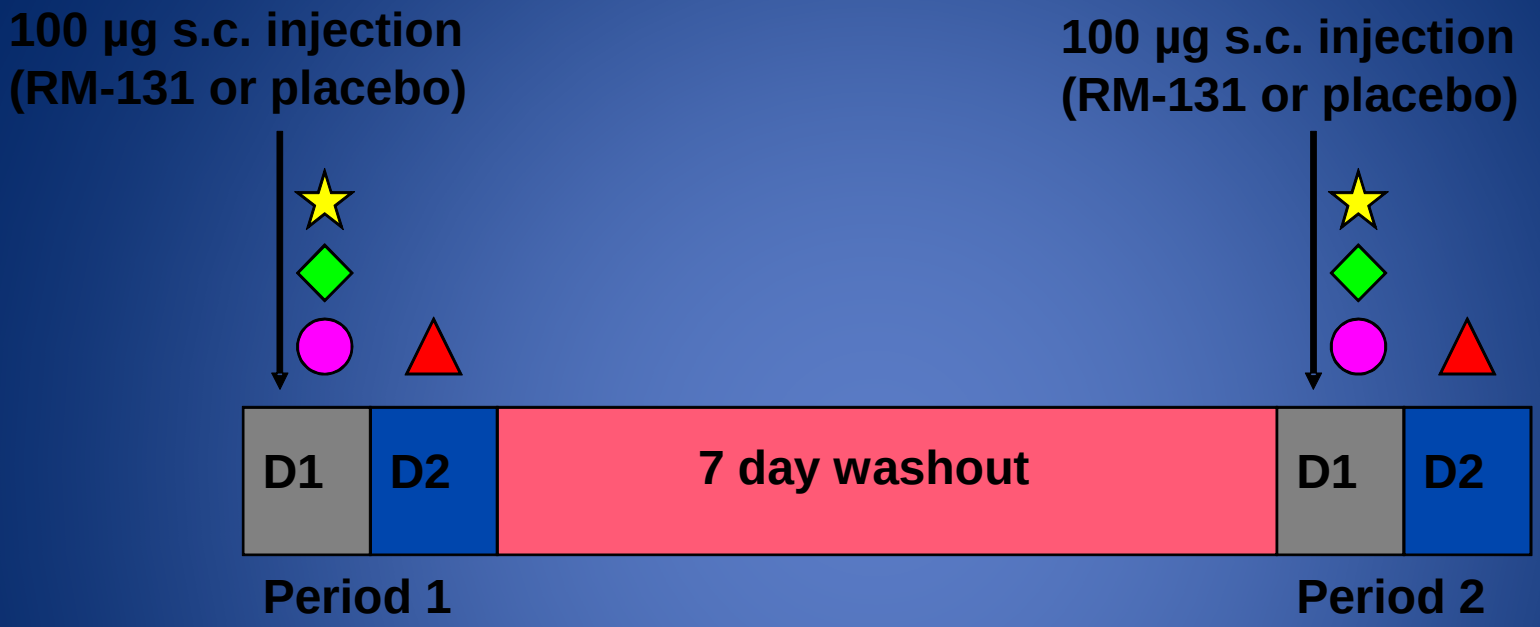
- **Primary objective:** To investigate the PD profile of a single dose of RM-131 in type 2 diabetes mellitus (T2DM) patients with gastrointestinal cardinal symptoms (GCSI) and prior documentation of DGE

- **Secondary objective:** To evaluate symptoms and safety of a single dose of RM-131 in T2DM patients with GCSI and prior documentation of DGE

Methods

- **Study Design:** Randomized, double-blind, placebo-controlled, single-dose, two-period, crossover study
- **Main eligibility criteria:**
  - T2DM with (a) documented DGE by scintigraphy or gastric emptying breath test and (b) ≥3 months history of symptoms of gastroparesis
  - Ages 18 to 60 years
  - Controlled T2DM (HbA1c <8.5%)
  - Stable concomitant medications
  - Prior exclusion of upper GI mechanical obstruction
  - BMI 18-40 kg/m^2
- PD profile, safety, and symptoms were assessed in both periods

Methods



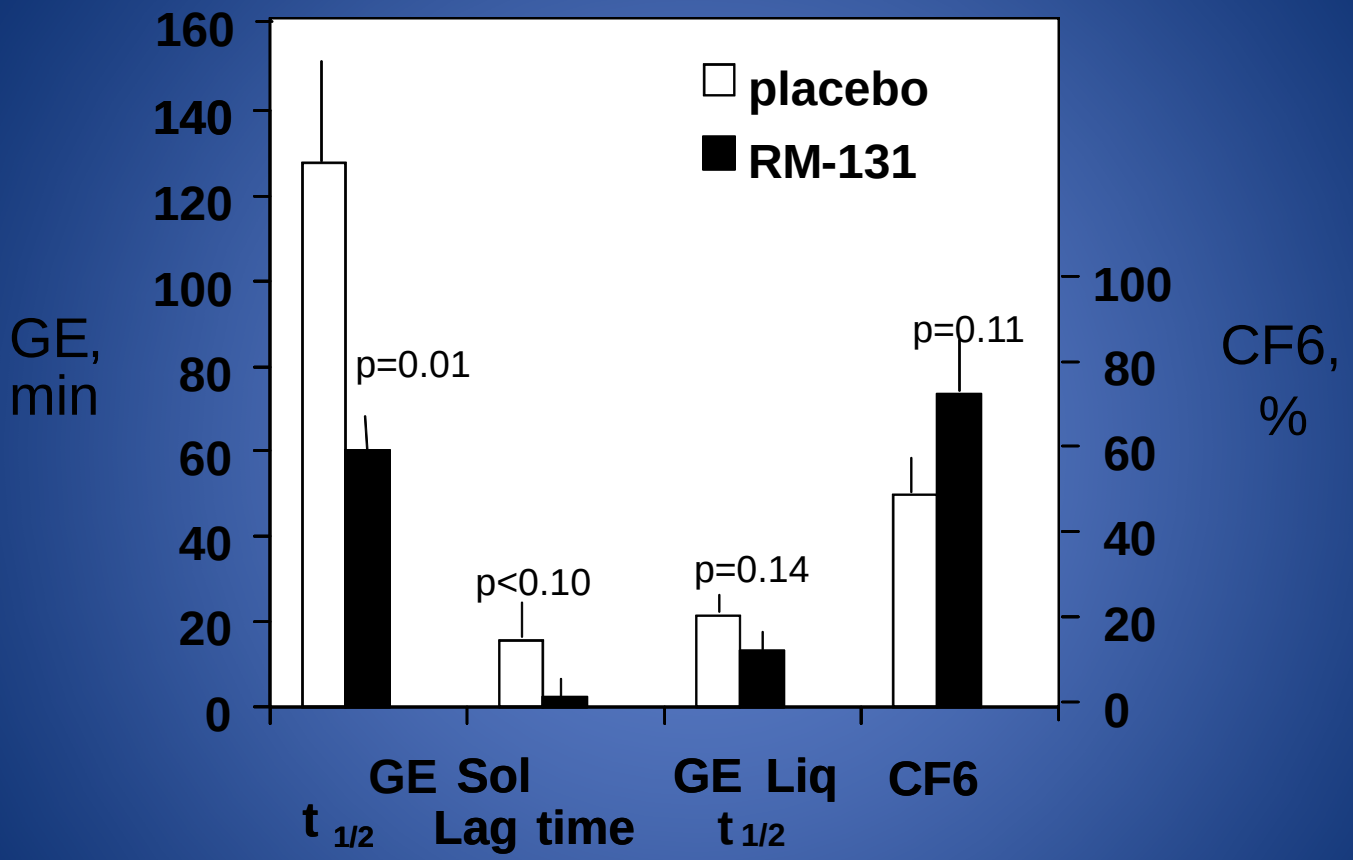
- GE (gastric emptying solids and liquids)
- CF6 (colonic filling % at 6h)
- Hormonal levels, safety, pharmacokinetic (PK) samples
- Symptoms

- Validated scintigraphy was used to assess GE and CF6 after a standardized meal 255 kcal meal (72% carbohydrate, 24% protein, 2% fat, and 2% fiber) given 30 min post-dosing

Patient Characteristics

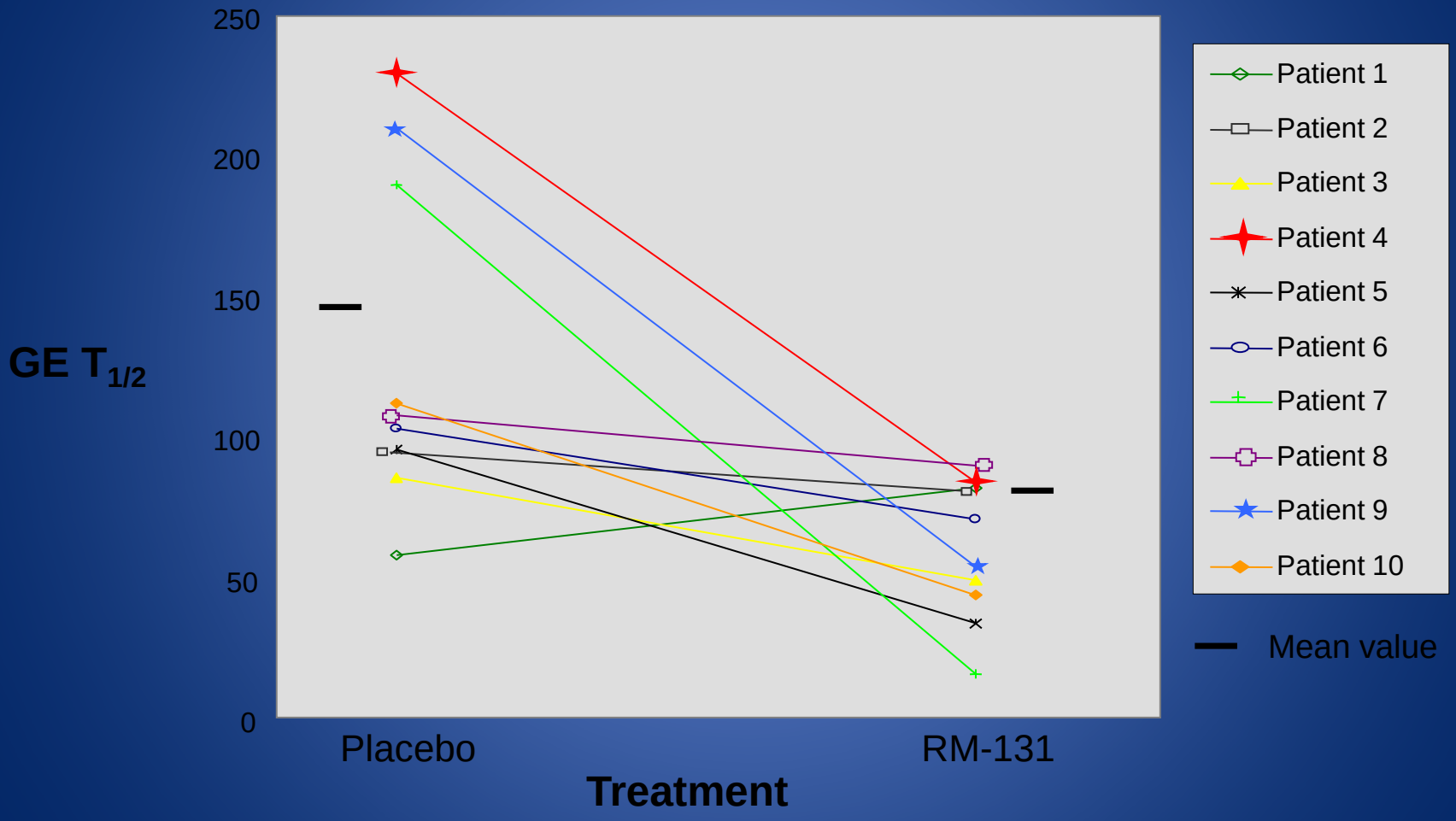
- All 10 patients in the study were female
- Mean values (±SEM) at study entry:
  - **Age (years)**: 51.8 (±2.5)
  - **BMI (kg/m^2):** 31.1 (±1.8)
  - **HbA1c (%):** 7.2 (±0.4)
  - **Total GCSI-DD score:** 1.32 (±0.2)

A single dose of RM-131 Decreases GE $T_{1/2}$ by 66%



- Effect of RM-131 on gastric emptying (solids and liquids) and colonic filling at 6 hours in all 10 patients

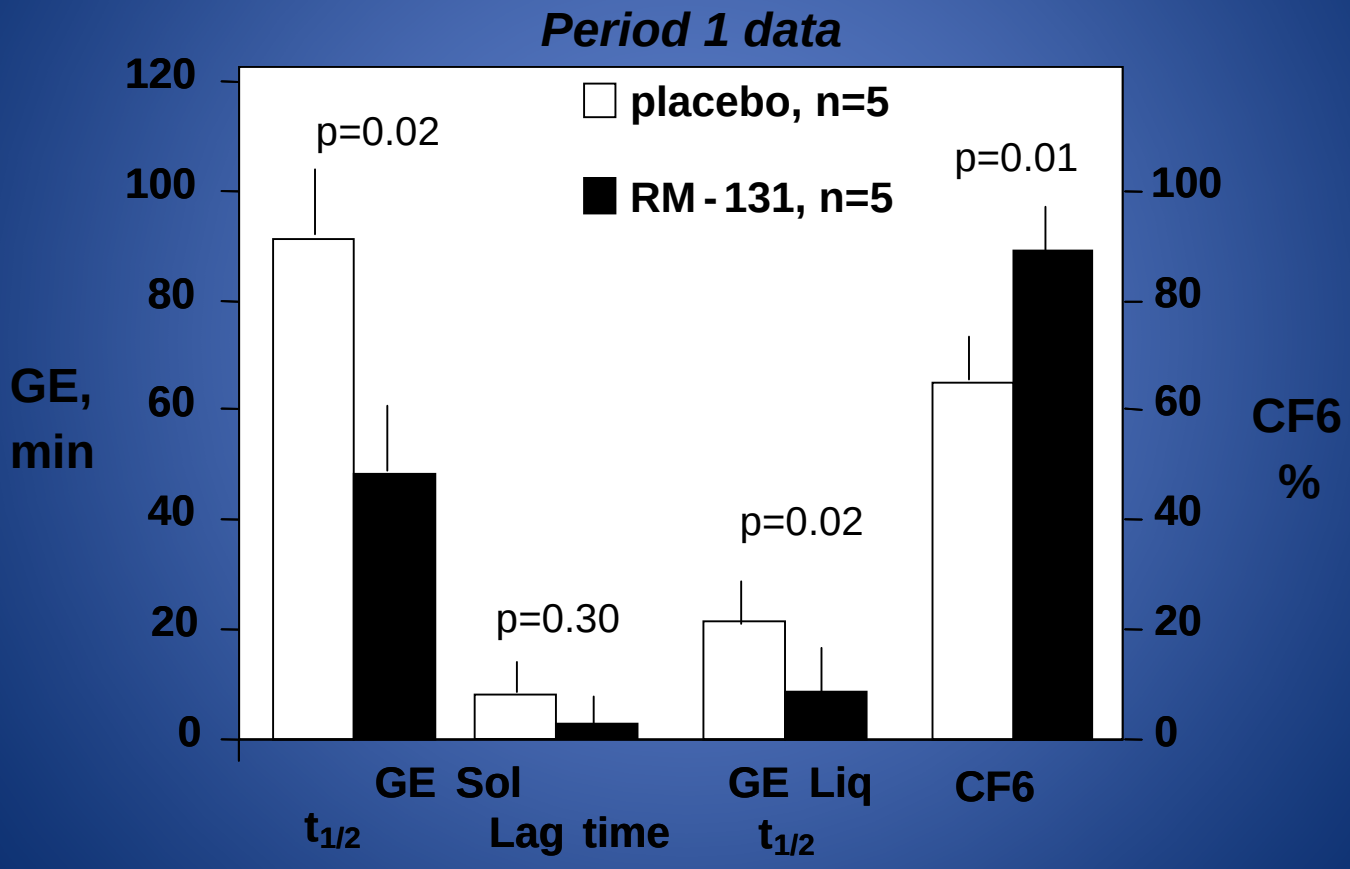
Accelerated GE $T_{1/2}$ in 9 of 10 Patients



Order Effect

- Effect of RM-131 on solid GE $T_{1/2}$ and CF6 larger when participant received RM-131 first
- Supportive analysis of Period 1 alone
  - Period 1 showed significant drug effects for GE $T_{1/2}$ and CF6.
  - Estimated ↓ in solid GE $T_{1/2}$ was 43 min (95%CI 10-75) or 61%.

RM-131 Modulates All Gastric and Small Bowel Transit Parameters in Period 1



Glycemic and Hormonal Effects

- **Glucose & Insulin:** Higher 120 minute blood glucose ($p=0.07$) with RM-131
  - No significant effects on insulin
- **Hormonal Effects:** Baseline hormone levels were not different on the two treatment days
  - Expected acute post-dose increases in 30-90 min AUC in GH, cortisol and prolactin levels with RM-131 were observed (all $p<0.02$)

Symptoms and Safety

- **Symptoms:** Single dose study, not designed nor powered to assess symptoms
  - No significant effects ($p>0.5$) on total GCSI-DD or composite score of nausea, bloating, postprandial fullness, and pain
- **Safety:** RM-131 was generally well tolerated
  - Total number of adverse events (AEs) ($p=0.016$) higher with RM-131, but none were serious
  - Light-headedness reported more often on RM-131
  - All AEs resolved spontaneously

Conclusions

- RM-131 greatly accelerates gastric emptying in patients with T2DM and delayed gastric emptying
- Overall, a 66% decrease in gastric emptying half time was observed
- Greatest improvement was observed in those with most abnormal gastric emptying
- Further clinical investigation of this promising and novel pharmacologic agent in the treatment of diabetic gastroparesis is needed

Ghrelin Agonist RM-131 Accelerates Gastric Emptying of Solids and Reduces Symptoms in Type 1 Diabetics: A Randomized Trial

Shin A, Camilleri M, Busciglio I, Burton D, Smith SA, Vella A, Ryks M, Rhoten D, Zinsmeister AR

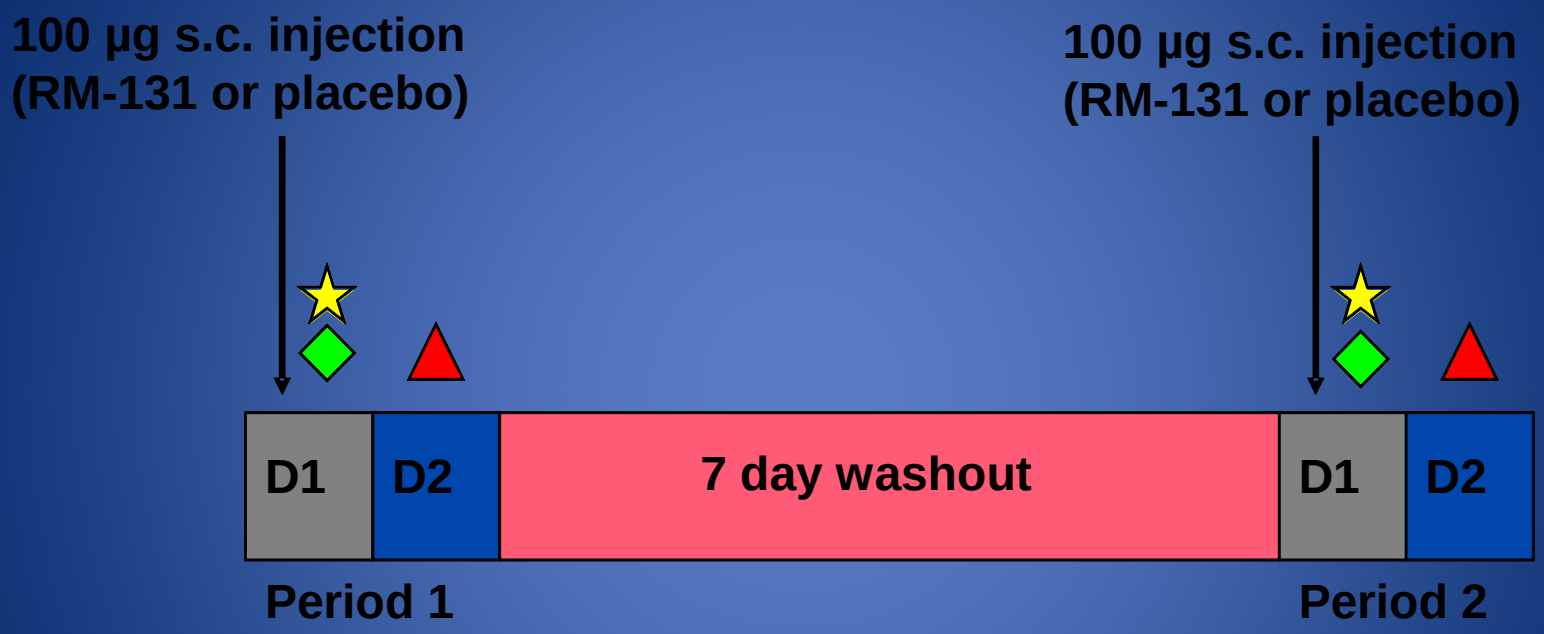
Objective

- To investigate the PD profile and effects on upper GI symptoms, safety and tolerability of a single dose of RM-131 in patients with type 1 diabetes mellitus (T1DM) and prior documentation of DGE

Methods

- **Study Design:** Randomized, double-blind, placebo-controlled, single-dose, two-period, crossover study
- **Eligibility criteria:** Males & females ages 18-65 years
  - T1DM with (a) documented DGE by scintigraphy or gastric emptying breath test and (b) ≥3 months history of symptoms of gastroparesis
  - HbA1c <10.1 %
  - Prior exclusion of upper GI mechanical obstruction
  - BMI 18-40 kg/m^2
- Medical records reviewed, baseline ECG obtained
- Enrolled and randomized by a computer-generated allocation schedule

Study Procedures

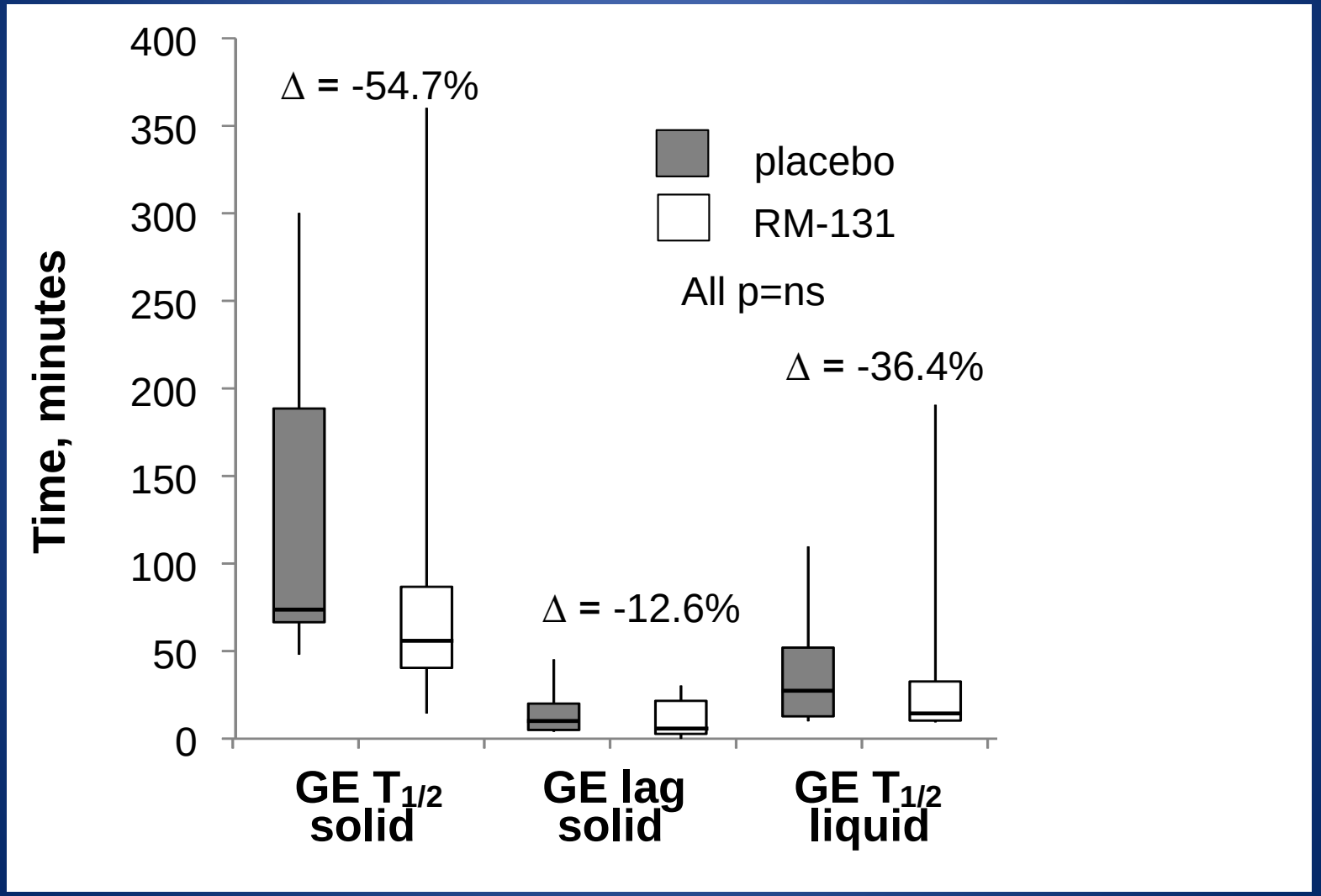


- GE (gastric emptying solids and liquids)
- CF6 (colonic filling % at 6h)
- Symptoms

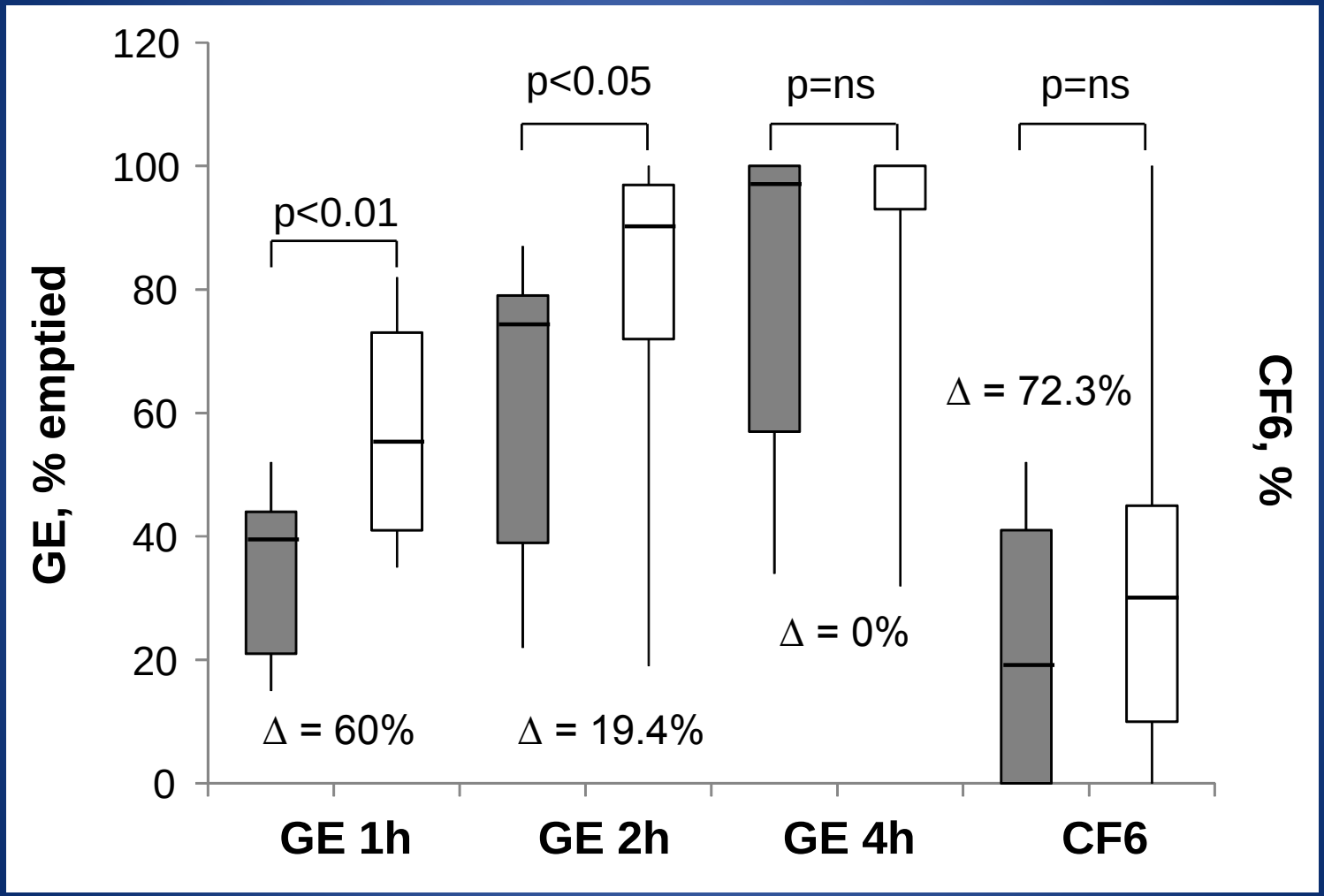
Patient Characteristics

- All 10 patients completed the study (2M, 8F)
- Mean values (±SEM) at screening:
  - **HbA1c:** 9.1±0.5%
  - **Age:** 45.7±4.4y
  - **BMI:** 24.1±1.1 kg/m^2
  - **Total GCSI-DD score:** 1.66±0.38 (median 1.71)
  - **Total NVFP score:** 1.73±0.39
- Absence of sinus arrhythmia observed in 6/10 patients, indicating the presence of cardiovagal dysfunction

Summary of the effects of RM-131 on GE for solids and liquids



Effect of RM-131 on %GE at 1, 2, 4 hours and CF6



Symptoms and Blood Glucose

Data show median (IQR)	Placebo	RM-131	P value	% Difference†
Total GCSI-DD average score	0.79 (0.75,2.08)	0.17 (0.00, 0.67)	0.041#	-125.0
Average score of combined nausea, vomiting, postprandial fullness, upper abdominal pain	1.00 (0.50, 2.00)	0.25 (0.00,0.50)	0.041#	-141.8
Blood glucose at 120 min, mg/dL	248 (182,273)	231 (152,290)	ns	-11.4

- †Median % difference among all participants for RM-131 minus placebo (within patient) relative to overall means (within patient); 100X [(within subject delta) / (within subject mean)]
- Data compared using Wilcoxon signed rank test or *paired t-test and #paired t test with Hochberg step-up correction; ns=not significant
- IQR=interquartile range

Safety

	Placebo (N)	RM-131 (N)	Severity as Described by Participant	Relation to Study Medication
Any adverse event	7	9	-	**possible**
Hyperhidrosis	0	2	moderate	**possible**
Fatigue	1	1	mild to moderate	**possible**
Abdominal pain	1	0	severe	**unlikely**
Irritation at injection site	0	1	mild	**likely**
Hunger*	0	5	mild to moderate	**possible**
Shakiness	0	1	moderate	**possible**
Euphoria	1	0	moderate	**unlikely**
Hyperglycemia	0	2	moderate to severe	**possible**
Hypoglycemia	1	0	mild	**possible**
Burning in feet	1	0	moderate	**unlikely**
Flank pain	1	0	mild	**possible**
Abdominal pressure	0	1	mild	**possible**
Flatulence	1	0	mild	**possible**
Borborygmi	**1**	**0**	**mild**	**possible**

*p=0.0625; all other p=ns (comparisons performed using McNemar's Test)

Conclusions

- Improvement in GE $T_{1/2}$ solid, GE 1h, and GE 2h in T1DM with RM-131
  - Comparable to the 66.1% in T2DM
- Significant improvement in total GCSI-DD and NVFP scores
- Appears effective in patients with cardiovascular neuropathy
- Further study of medium/long-term efficacy

Lembo et al. DDW 2014

- Phase 2 RCT to investigate safety and efficacy of RM-131 in patients with diabetic gastroparesis
- Design: 1 week single-blind pcbo run-in followed by randomization to pcbo vs. RM-131 (10 ug SC BID or 10 ug SC QD).
  - GE breath test at baseline and at 28 days
  - Daily symptom diary (nausea, pain, bloating, earlying satiety)
- Results: 204 patients randomized (32.3%M, mean age 55.1 y, mean BMI 32.6 kg/m2, 11.9% Type 1 DM)
  - Relamorelin (10 μg BID), resulted in significant acceleration of gastric emptying ($p < 0.03$)
  - Significant improvements in vomiting endpoints on relamorelin treatment compared to placebo

Future Directions

- Larger sample sizes
- Evaluate medium to long-term effects and safety
- Efficacy among patients with moderate to severe gastroparesis
- Other conditions such as idiopathic gastroparesis, post-surgical or post-vagotomy gastroparesis, post-operative ileus, or chronic constipation

Acknowledgements

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