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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Motility Conference

2/4/15
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\textsuperscript{1,2}
  - Poorer glycemic control
  - Anxiety, depression, and neuroticism\textsuperscript{3}
- More likely to have cardiovascular disease, nephropathy, hypertension, retinopathy\textsuperscript{4}

\textsuperscript{1} Bytzer P et al. Arch Intern Med 2001
\textsuperscript{2} Maleki D et al. Arch Intern Med 2000
\textsuperscript{3} Talley NJ et al. Am J Gastroenterol 2001
\textsuperscript{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

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

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

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What level of hyperglycemia is important?

- Bytzer et al. Am J Gastroenterol 2002
- Hasler WL et al. Gastro 1995
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

<table>
<thead>
<tr>
<th>Merit/limitation</th>
<th>Merit/Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td>Direct measure of GE</td>
<td>Limited access to gamma-camera</td>
</tr>
<tr>
<td>Quantitative assessment</td>
<td>Lack of adherence to standardized protocol</td>
</tr>
<tr>
<td>Assess GE both solids and liquids</td>
<td>Significant intra-individual CV (24%)?</td>
</tr>
<tr>
<td>Characterize intragastric distribution of contents</td>
<td>Limitations of low-fat, low-fiber meal</td>
</tr>
</tbody>
</table>
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.
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 \( T_{1/2} \) utilizing \( ^{13} \text{C}- \)Octanoate breath test (350 kcal, 7g fat meal)

<table>
<thead>
<tr>
<th></th>
<th>10 mg TZP-102</th>
<th>20 mg TZP-102</th>
<th>40 mg TZP-102</th>
<th>All TZP-102</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (Day -16 to -7)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( N )</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>( \text{Mean (SD)} )</td>
<td>216.9 (66.7)</td>
<td>215.6 (55.3)</td>
<td>207.4 (36.9)</td>
<td>213.0 (52.4)</td>
<td>224.1 (57.4)</td>
</tr>
<tr>
<td><strong>Day 28</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>( N )</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>( \text{Mean (SD)} )</td>
<td>197.2 (54.8)</td>
<td>186.4 (65.6)</td>
<td>170.2 (30.5)</td>
<td>183.9 (51.5)</td>
<td>179.9 (55.6)</td>
</tr>
<tr>
<td><strong>Day 28 CFB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>( N )</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>( \text{Mean (SD)} )</td>
<td>-19.7 (57.2)</td>
<td>-29.2 (48.1)</td>
<td>-37.2 (36.98)</td>
<td>-29.1 (46.97)</td>
<td>-44.2 (46.0)</td>
</tr>
<tr>
<td>( P )-value (vs Placebo)</td>
<td>0.325</td>
<td>0.639</td>
<td>0.864</td>
<td>0.606</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** TZP-102 for 28 days, at doses of 10-40mg once daily, does not accelerate gastric emptying but it 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

<table>
<thead>
<tr>
<th></th>
<th>10 mg TZP-102</th>
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<th>20 mg TZP-102</th>
<th>20 mg TZP-102</th>
<th>20 mg TZP-102</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>BL</td>
<td></td>
<td></td>
<td></td>
<td>BL</td>
<td>Week 12</td>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Δ from BL</td>
<td></td>
<td></td>
<td></td>
<td>Δ from BL</td>
<td>BL</td>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSDD Composite score</td>
<td>3.5±0.6</td>
<td>1.8±1.2</td>
<td>-1.7±1.2</td>
<td>3.7±0.6</td>
<td>2.2±1.3</td>
<td>-1.4±1.3</td>
<td>3.6±0.6</td>
<td>2.1±1.1</td>
<td>-1.5±1.2</td>
</tr>
</tbody>
</table>

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 $\geq 10 \, \mu g$
    - Maximal effect at 100 $\mu g$ dose level
Randomized Controlled Phase Ib Study of Ghrelin Agonist, RM-131, in Type 2 Diabetic Women with Delayed Gastric Emptying: Pharmacokinetics and Pharmacodynamics

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/m²

• PD profile, safety, and symptoms were assessed in both periods
Methods

- 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.

100 µg s.c. injection (RM-131 or placebo)

Period 1

100 µg s.c. injection (RM-131 or placebo)

Period 2

- 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/m²): 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

Period 1 data

- GE, min
  - Sol: p=0.30
  - Lag time: p=0.02
  - GE t_{1/2}: p=0.02
  - CF6: p=0.01

- Placebo, n=5
- RM-131, n=5
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

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/m²

• Medical records reviewed, baseline ECG obtained

• Enrolled and randomized by a computer-generated allocation schedule
Study Procedures

100 µg s.c. injection (RM-131 or placebo)

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

Period 1:

D1 D2

7 day washout

Period 2:

D1 D2

100 µg s.c. injection (RM-131 or placebo)
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/m²
  – **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

\[ \Delta = -54.7\% \]

\[ \Delta = -12.6\% \]

\[ \Delta = -36.4\% \]

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

- GE, % emptied
- CF6, %

- GE 1h: ∆ = 60%
- GE 2h: ∆ = 19.4%
- GE 4h: ∆ = 0%
- CF6: ∆ = 72.3%

p < 0.01, p < 0.05, p = ns
## Symptoms and Blood Glucose

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

- †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

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

*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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