A Phase II, Single-Center, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Parallel-Group Study to Evaluate the Pharmacodynamics of RM-131 in Patients with Chronic Constipation

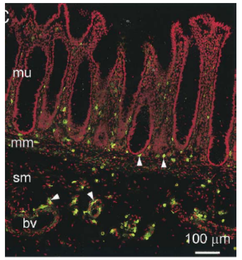
Andres Acosta, Gururaj Kolar, Johanna Iturrino, Lawrence Szarka, Amy Boldingh, Duane Burton, Michael Ryks, Deborah Rhoten, Alan R. Zinsmeister[#], Michael Camilleri.

Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.), Division of Gastroenterology and Hepatology, Department of Medicine

[#] Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota

Background

- Chronic constipation is highly prevalent among adults.
- Some patients do not achieve satisfactory relief of chronic constipation
- Ghrelin is 28 amino acid, octanolyated gastrointestinal (GI) hormone and an endogenous ligand of the Ghrelin receptor (GHS-R)
- Ghrelin receptor is expressed through-out the gastrointestinal tract, including the colon.
- Actions of ghrelin include acceleration of gastric emptying and increase in appetite.
- RM-131 is a pentapeptide, selective ghrelin receptor 1a agonist.
- RM-131 accelerated gastric emptying in patients with diabetes mellitus.
- However, it is unclear if a ghrelin agonist will increase colonic motility.



The arrows indicate entero-endocrine and/or mast cells.

N. B. Dass et al. Neuroscience (2003)

Aim

To evaluate effects of the ghrelin agonist, RM-131, on gastric emptying (GE), small bowel transit (SBT) and colonic transit (CT) in patients with chronic constipation.

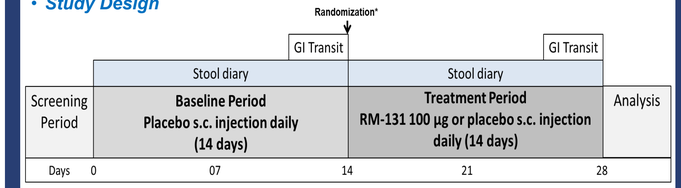
Methods (1)

***Study Design*:**

- In a single-center, randomized (1:1), double-blind, placebo - controlled, parallel-group study involving single daily dose administration over 14 days, we evaluated the effect of 100µg of RM-131 S.C. once daily for 14 days, on GE, SBT, and CT in patients with chronic constipation.
- The data shown is a sub-study (pharmacodynamics) that is part of a 48 patient study to evaluate the efficacy of RM-131 in chronic constipation on clinical end-points.
- During the14-day baseline placebo-treatment period, and the 14-day double-blind active treatment period, daily diaries of bowel functions, abdominal symptoms, global assessments and baseline CT were collected

Methods (2)

- ***Study Design***

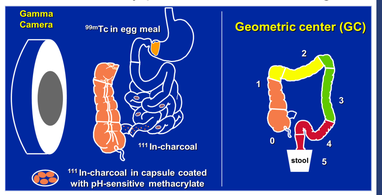


* Only in patients with GC24h less than GC<2.4 were selected for treatment period.

- ***Eligibility Criteria:***
  - Chronic (idiopathic) constipation by Rome III criteria;
  - Age:18-65 years old, body mass index (BMI) of 18-40 kg/m^2,
  - Baseline CT with geometric center (GC) < 2.4 at 24 hours,
  - Average spontaneous BMs ≤4/week
  - No evidence of a rectal evacuation disorder
- ***Sub-study for pharmacodynamics (PD) in Gastrointestinal and Colonic Transit (CT):***

Sub-study end-points: CT at the end of treatment period Geometric center (GC) of colonic counts for solids at 4, 8, 24, 32 and 48 h; ascending colon emptying ($T_{1/2}$), GE and SBT. SBT is measured by percent of colonic filling at 6hrs (CF6%).

Transit of solids was measured by validated scintigraphic method at baseline from Days 12-14 and over 48-h period on Days 26-28. The 24h image was obtained before medication on treatment day 13.



- ***Safety:***

Safety was evaluated including adverse events, 12-lead electrocardiogram, and clinical laboratory assessments.

- ***Statistical Analysis:***

The primary efficacy analysis (for CT and GE parameters) was by analysis of covariance (ANCOVA) models using baseline measurements (GC24 for CT data; BMI for SBT and AC T½; and age for GE) as covariates.

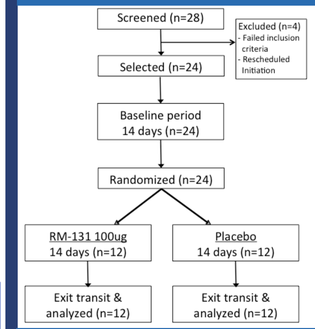
- ***Statistical Power:***

The PD sub-study required 12 patients per arm to detect a 37% difference in the colonic GC at 24h.

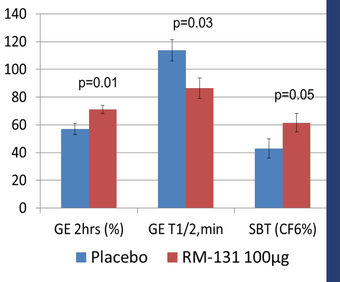
Results:

Demographics	Placebo	RM-131 100µg
Participants with Chronic constipation (N)	12	12
Age (y)	41.75 ± 2.9	40.1 ± 3.0
BMI (Kg/m2)	24.9 ± 1.0	25.5 ± 1.0
Gender (F)	12	12
Baseline GC24	1.95 ± 0.1	1.74 ± 0.1

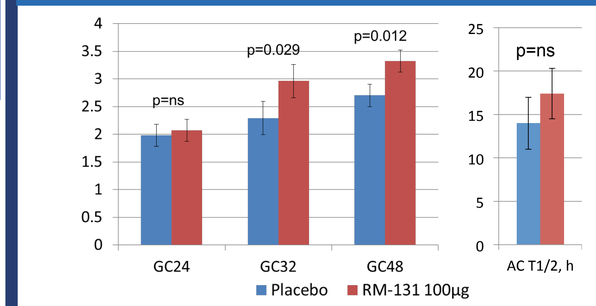
CONSORT Flow Diagram



Effect of RM-131 in Gastric Emptying (GE), and Small Bowel Transit (SBT)



Effect of RM-131 in Colonic Transit (CT)



Adverse Events

- There were no drop outs or withdrawals;
- AEs were generally balanced between groups, except that hunger / increased appetite was more frequent on RM-131 (6/12) compared to placebo (0/12; p=0.012).

Summary of Results

- RM-131 was associated with:
  - a significant acceleration of gastric emptying (GE T½ p=0.03),
  - a significant acceleration of colonic filling at 6h [CF6%, a surrogate for Small Bowel Transit), p=0.05]
  - a significant acceleration of colonic transit (CT) at GC32 and GC48h (p=0.029 and p=0.012, respectively).
- There were no significant increases in CT at GC24h (p=0.44) or ascending colon emptying (AC T½ p=0.43).
- Clinical endpoints will be analyzed upon completion of the 48th participant in the overall study.

Discussion and Conclusions

- RM-131, 100µg S.C. daily, significantly accelerates colonic transit in patients with chronic constipation, in addition to accelerating SBT and GE, demonstrating stimulation of both upper and lower GI motility.
- In prior studies (*Deiteren et al NGM 2010*), the observed magnitude of effect on colonic transit at 48 h was associated with a 1 point difference in stool consistency on the Bristol Stool Form scale.
- These data suggest that the PD effect observed with RM-131 is likely to be clinically relevant to increase bowel movements in patients with chronic constipation.

References:

1. Deiteren, A., Camilleri M, et al. (2010). Neurogastroenterology and motility **22**: 415.
2. Dass, N.B, Munonyara, M. et al., (2003) Neuroscience. 120: 443-53.

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