Phase 1, Randomized, Placebo-Controlled, Single-Dose, Two-Period, Crossover Study of RM-131 on Pharmacodynamics and Symptoms in Type 1 Diabetics with Documented Delayed Gastric Emptying

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Background

Ghrelin is an endogenous ligand for GHS-1a receptor and a potential treatment for delayed gastric emptying (DGE). RM-131 is a synthetic ghrelin agonist which we had previously shown greatly accelerates solid gastric emptying (GE) in type 2 diabetics with DGE.

Aim

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

Methods

Study Design: In a randomized, double-blind, placebo-controlled, single-dose, two-period, crossover study with a 7-day washout, 10 patients with T1DM and prior DGE received RM-131 (100µg s.c.) or placebo. Eligibility was confirmed by medical history, physical examination, concomitant medication review, clinical laboratory tests, and a 12-lead electrocardiogram (ECG).

Period 1: Patients received RM-131 (100µg s.c.) or placebo.

Period 2: Patients received the alternative therapy after a 7-day washout.

PD profile, safety, and symptoms were assessed in both periods.

Main eligibility criteria: Adult patients with DGE, glycosylated hemoglobin (HbA1c) <10.1%, stable concomitant medications, prior exclusion of upper GI mechanical obstruction, and BMI 18-40 kg/m^2.

PD profile: Using a solid-liquid radiolabeled meal and scintigraphy, we assessed GE over 4 hours and colonic filling at 6 hours (CF6); the meal was ingested 30 minutes after study drug administration.

Safety: Adverse events and vitals were assessed in both periods.

Symptoms: We assessed upper GI symptoms using a daily gastroparesis cardinal symptom index (total GCSI-DD) and a combination of nausea, vomiting, fullness and pain (NVFP) using a 0-5 scale.

Statistical Considerations: Data summarized as median and interquartile range (IQR) due to non-normally distributed data, with the exception of GE at 1 and 2 hours, GCSI-DD and NVFP scores.

Summary of Results

- ***Patient Characteristics:*** Among the 10 participants (2 male, 8 female) average values at study entry were: HbA1c 9.1 ± 0.5 (SEM)%; age 45.7 ± 4.4 years; BMI 24.1 ± 1.1 kg/m^2; total GCSI-DD score 1.66 ± 0.38; total NVFP score 1.73 ± 0.39. Absence of sinus arrhythmia on baseline ECG was observed in 6/10 patients.
- ***Primary Endpoint - Effect on Transit:*** RM-131 decreased mean solid GE $T_{1/2}$ by -33.8 minutes (p=ns). Median solid GE $T_{1/2}$ was faster by -33.9 min (p=ns) for RM-131 compared to placebo [interquartile range (IQR) -12, -49]; a 54.7% decrease (Table 1 & Figure 1).
- RM-131 decreased gastric retention of solids at 1 (p=0.003) and 2 (p=0.019) hours with a mean difference of 24.7 [±14.7(SEM)%] relative to overall mean at 2 hours.
- The presence of vagal dysfunction did not module the effect of RM-131 on transit.
- Numerical differences in lag time for GE solids, GE $T_{1/2}$ liquids and CF6 solids (Table 1) were not statistically significant.
- ***Order Effect:*** No significant order effect was seen.
- ***Glucose & Insulin:*** No significant effects on blood glucose at 120 minutes were seen.
- ***Symptoms:*** While patients participating in the study had generally lower symptom scores than at screening, we observed a significant reduction in total GCSI-DD (Hochberg adjusted p=0.041, p=0.026 by paired t-test) and NVFP scores (Hochberg adjusted p=0.041, p=0.041 by paired t-test) with RM-131 when compared to placebo. (Table 1).
- ***Safety:*** RM-131 was generally well tolerated. There were no significant adverse effects.

Effect of RM-131 on Gastric Emptying (GE) of solids and liquids

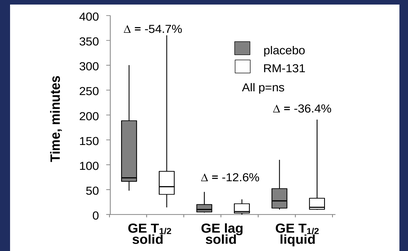

Figure 1. Gastric emptying (GE), minutes for solids and liquids. Data are median (IQR, range); RM-131 compared to placebo by Wilcoxon signed rank test; Δ=median % difference for each endpoint.

Accelerated GE $T_{1/2}$ in 8 of 10 Patients

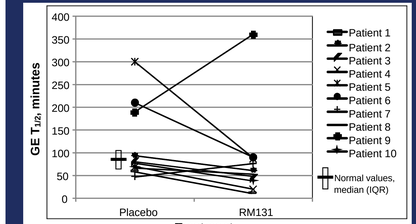

Figure 3. Individual Patient Data. Change in GE $T_{1/2}$ solid by treatment period for each individual patient [gastric emptying (GE), minutes for solids for all 10 patients by treatment period].

RM-131 significantly accelerates early stages of GE

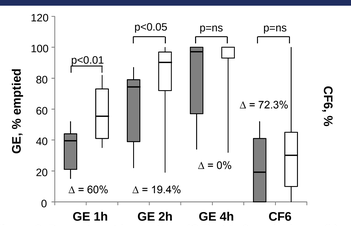

Figure 2. Percent gastric emptying (GE) at 1, 2, and 4 hours (h), and colonic filling (CF6) at 6h. Gray=placebo; white=RM-131. Data are median (IQR, range); p values by Wilcoxon signed rank or paired t test (GE 1h and 2h) comparing RM-131 versus placebo; Δ=median % difference. Data not available in one participant for GE 1h.

GE of solids in one individual patient

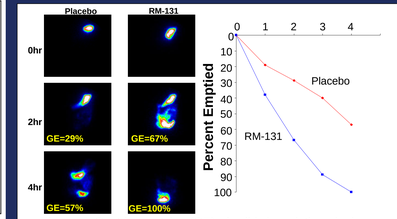

Figure 4. Gastric emptying (GE) of solids by scintigraphy in one patient showing delayed GE with placebo and normal GE with RM-131 (left); GE shown as percent emptied over time for placebo and RM-131 in the same individual (right).

Table 1: Main Transit, Symptom and Glycemic Indicators in all 10 Patients

Data show median, IQR (N=10)	Placebo	RM-131	p value	Percent Difference†
GE $T_{1/2}$ solid, minutes	75.7 (66.4, 188.6)	58.2 (40.4, 86.6)	ns	-54.7
GE solid lag time (t10% GE), minutes	9.0 (5.0, 20.0)	5.9 (2.8, 21.4)	ns	-12.6
GE at 1h (%)	40.3 (21.0, 44.4)	55.6 (40.5, 73.1)	0.005*	60.0
GE at 2h (%)	74.6 (38.5, 79.4)	88.7 (72.2, 97.4)	0.019*	19.4
GE at 4h (%)	97.1 (57.2, 100)	100 (92.9, 100)	ns	0
GE $T_{1/2}$ liquid, min	26.4 (12.7, 51.92)	13.0 (10.4, 32.6)	ns	-36.4
CF6 solid, %	19.0 (0.0, 41.0)	28.5 (10.0, 45.0)	ns	72.3
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; one participant had missing 1 hour gastric emptying data at both study visits; ns=not significant

IQR=interquartile range; GE=gastric emptying; CF6=colonic filling at 6 hours

Conclusions

• RM-131 significantly accelerates early GE of solids and reduces upper GI symptoms in patients with type 1 diabetes mellitus (DM) and delayed gastric emptying.

•The magnitude of the effect in type 1 DM is in the range observed in type 2 DM and does not appear to be dependent on normal vagal function.

•A limitation of the study is the small sample size, and statistical inferences should be interpreted with caution.

•A larger sample size will be required to assess the generalizability of the data.

•RM-131 deserves further study of its medium and longer term efficacy in diabetic patients with upper GI symptoms and DGE of solids.

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