Digestive Disease Week 2011

RM-131: A Potent Gastroprokinetic Agent

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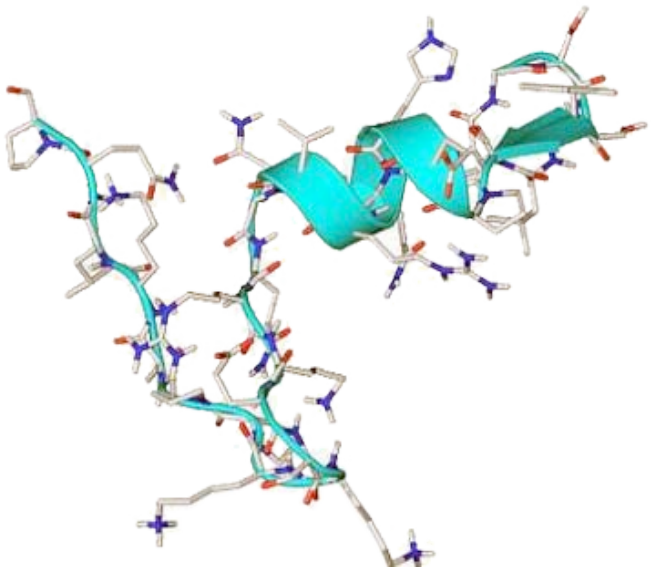
Ipsen Biopharmaceuticals
Milford, Massachusetts, USA and Les Ullis, France

May 7, 2011

Presented by Lee M. Kaplan, Massachusetts General Hospital
Chair, Scientific Advisory Board, Rhythm Pharmaceuticals

Ghrelin



- 28 amino acid acylated peptide
- Secreted primarily from gastric mucosa
  - Also duodenal mucosa and CNS
- Binds to growth hormone secretagogue (GHS) 1a receptor
- Activities:
  - Stimulates GH secretion
  - Increases food intake
    - Increases body fat
    - Increases lean mass
  - Increases GI motor function
    - Promotes gastric emptying
    - Stimulates intestinal motility
  - Anti-Inflammatory

RM-131: Ghrelin Peptide Agonist

- Pentapeptide
- Design optimized for pharmacologic activity (weight gain)
- High potency (~10-fold more potent than ghrelin in activating GHS-1a receptor)
- Long circulating half-life (~10-fold longer than ghrelin in rat)
- Increases GH secretion
- Increases food intake and body weight
- Anti-inflammatory: TNBS model of colitis
- Increases GI motility

Aims

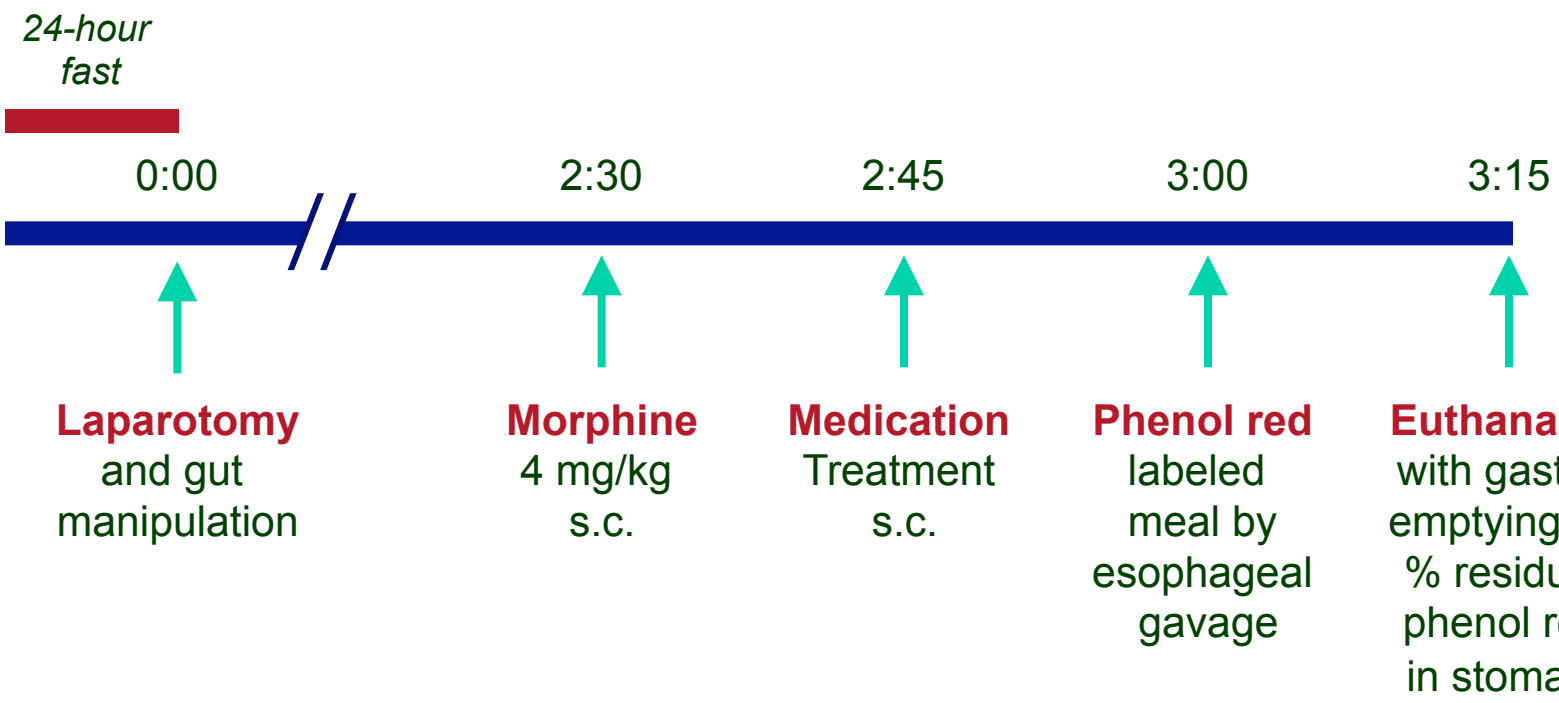
- To determine the gastric prokinetic effects of RM-131, a novel ghrelin agonist, in a rodent model of GI dysmotility
- To compare the gastric prokinetic profiles of a variety of newly developed ghrelin agonists in this model

Recently Developed Ghrelin Mimetics

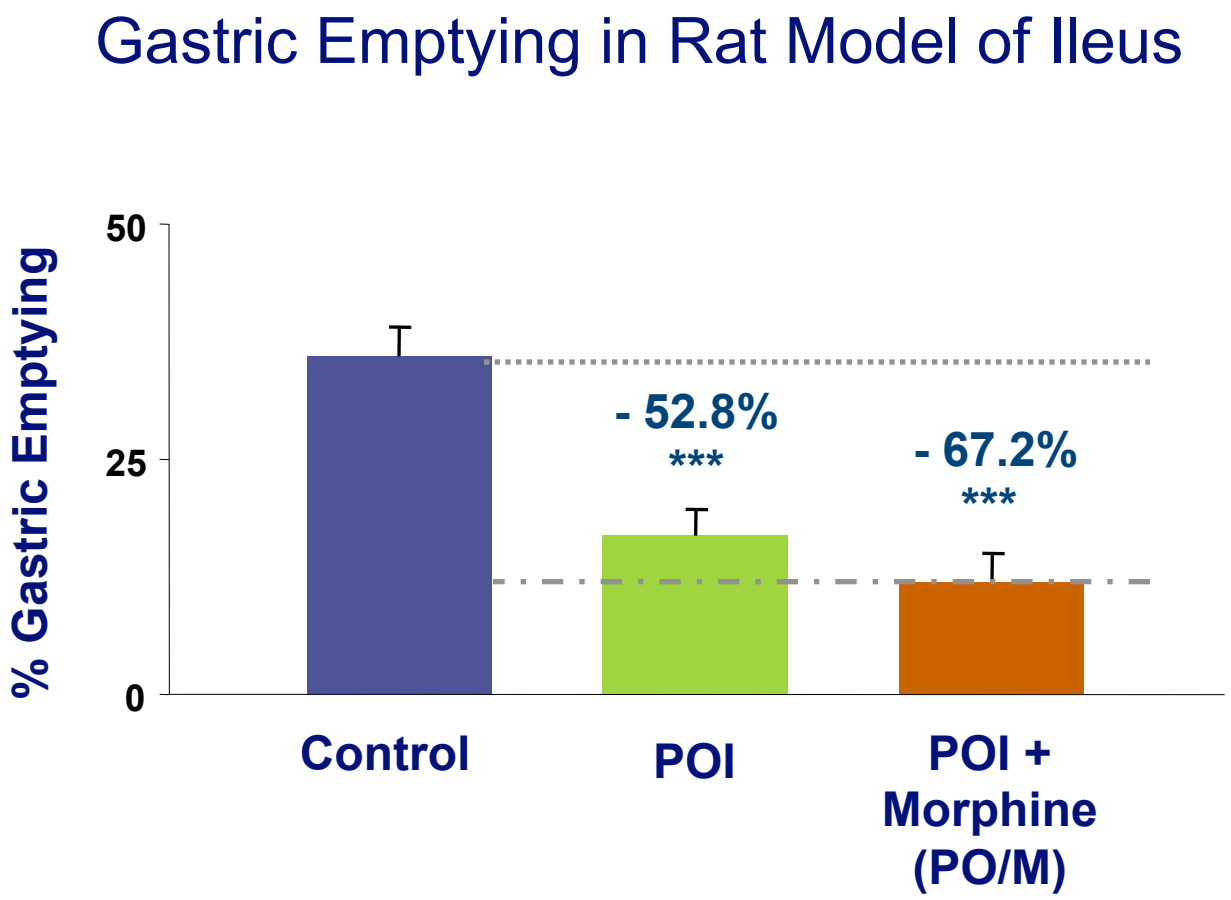
Compound	Type	Optimized for:
Ghrelin	Peptide	Natural hormone
MK-677	Small molecule	GHS1a activity
Ipamorelin	Peptide	GHS1a activity
Anamorelin	Small molecule	GHS1a activity
RM-131	Peptide	Physiological endpoint (weight gain)

Study Design – Postoperative Ileus + Morphine

Male Sprague-Dawley Rats

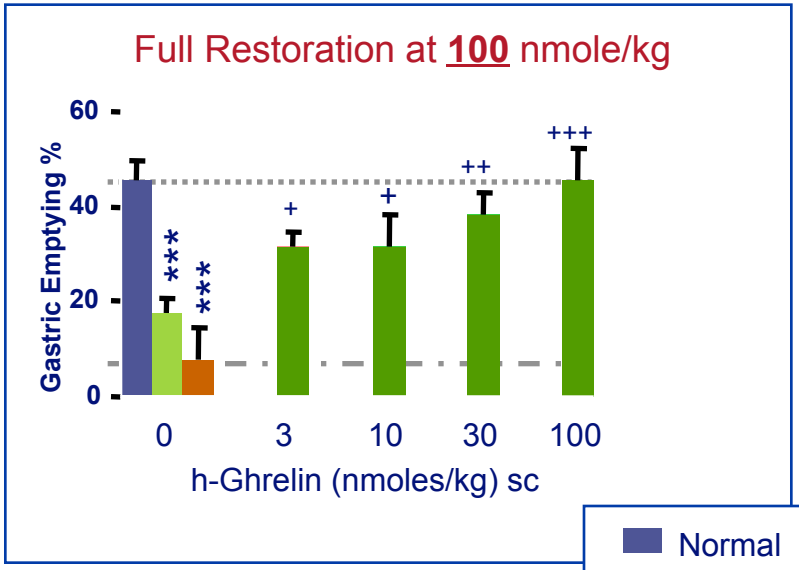


POI and Morphine (PO/M) Inhibit Gastric Motility



RM-131 vs. Ghrelin on Gastric Emptying After PO/M

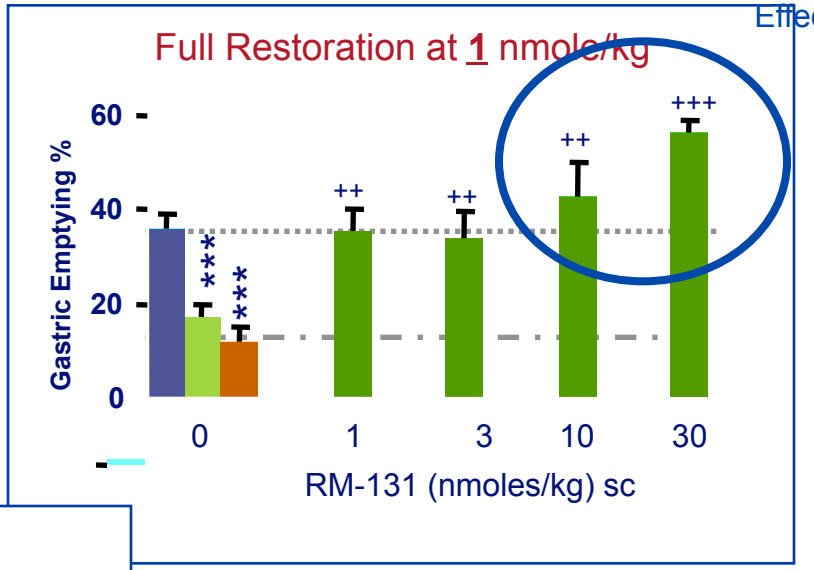
h-Ghrelin



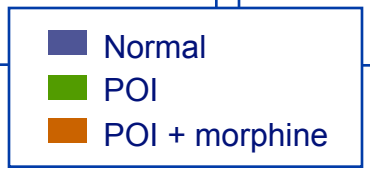
ED_{50}: 4.04 nmole/kg

RM-131

Supraphysiological Effect



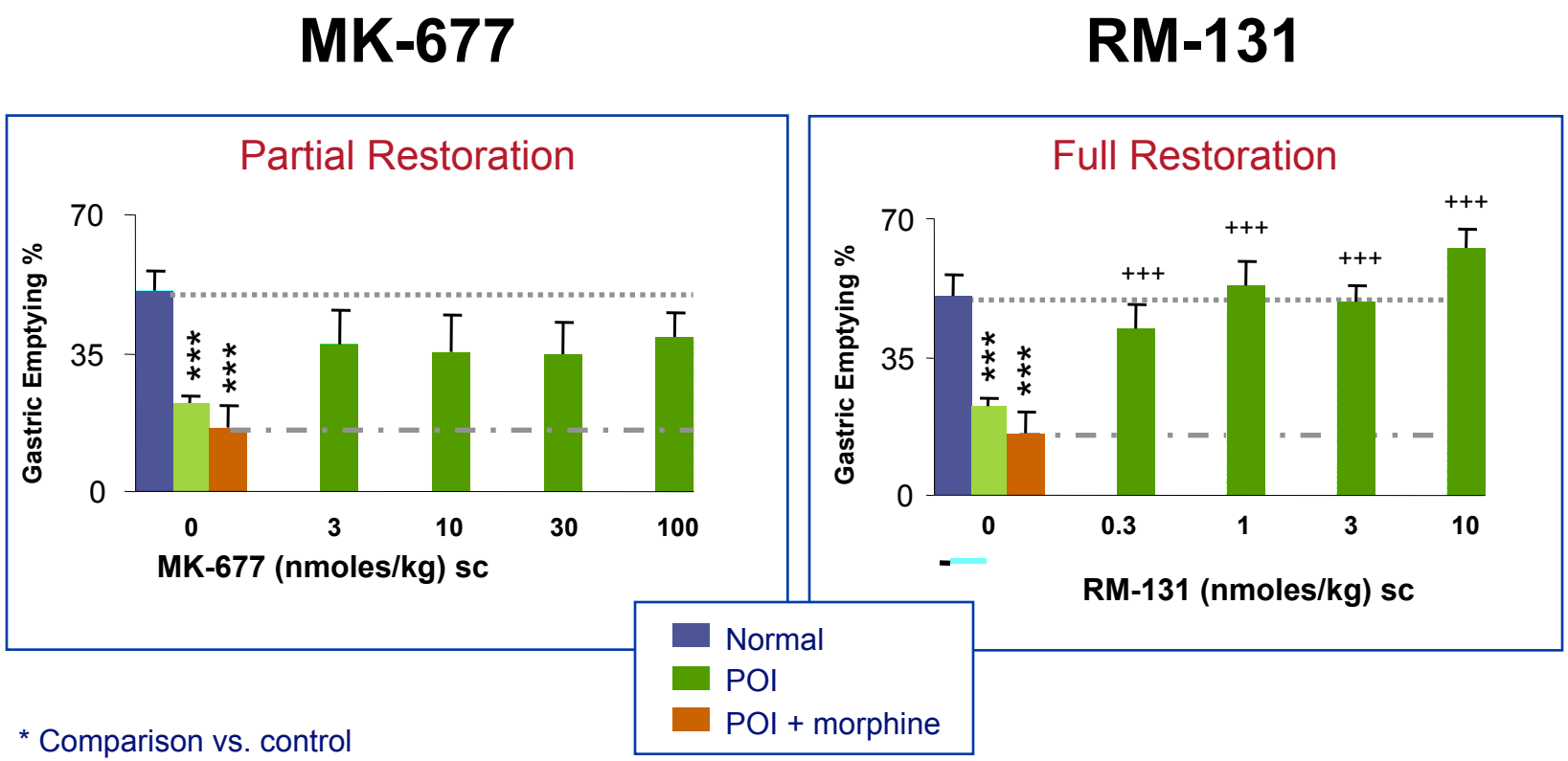
ED_{50}: 0.03 nmole/kg



* Comparison vs. control
\+ Comparison vs. PO/M

RM-131 is 100-fold more potent in enhancing gastric emptying than native human ghrelin

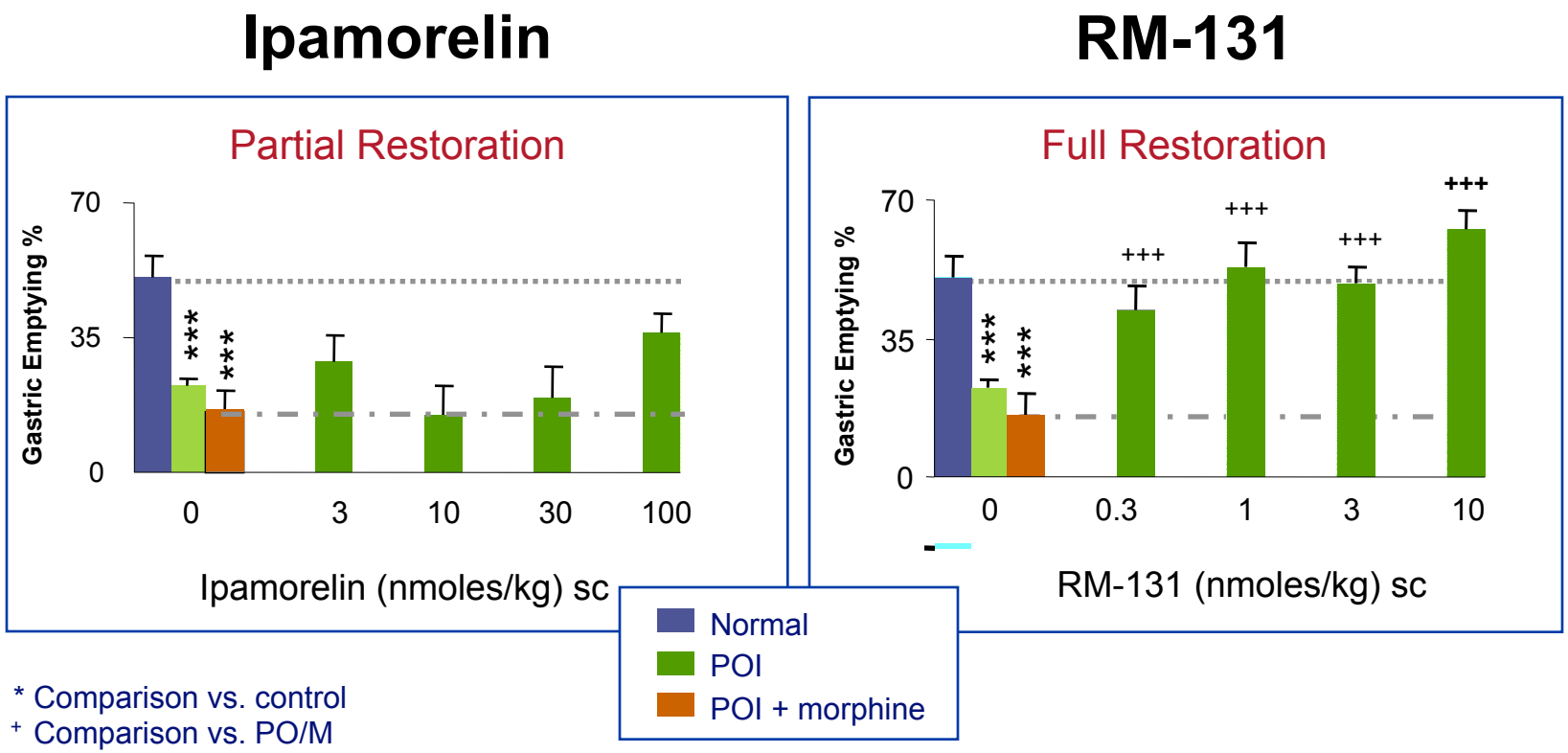
RM-131 vs. MK-677 on Gastric Emptying After PO/M



* Comparison vs. control
\+ Comparison vs. PO/M

MK-677 induces partial restoration of gastric emptying

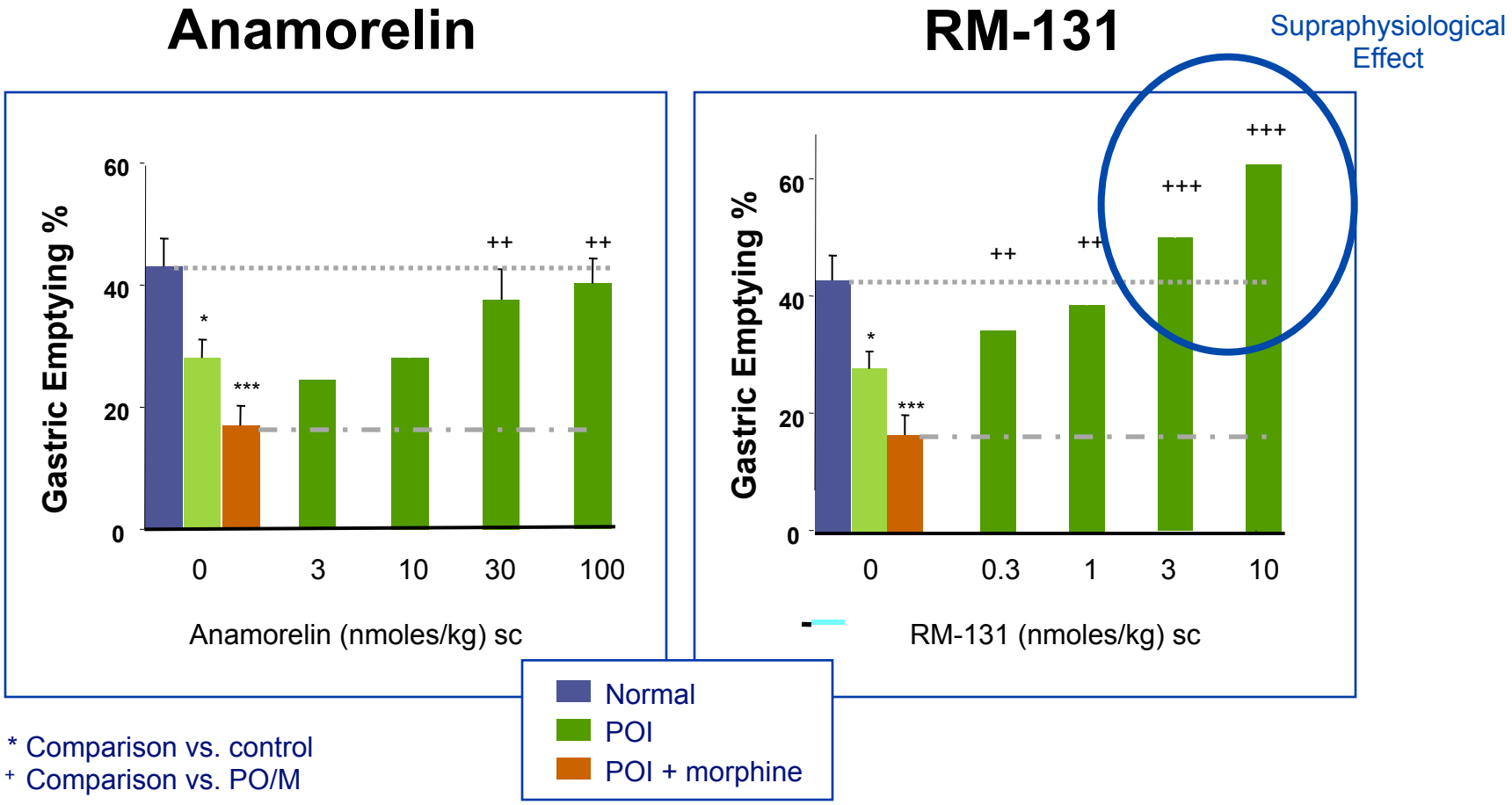
RM-131 vs. Ipamorelin on After PO/M



* Comparison vs. control
\+ Comparison vs. PO/M

Ipamorelin induces partial restoration of gastric emptying

RM-131 vs. Anamorelin on After PO/M



* Comparison vs. control
+ Comparison vs. PO/M

Anamorelin restoration of gastric emptying requires 100-fold higher molar dose than RM-131

Summary and Conclusions

- A rat model of Ileus Induced by laparotomy and morphine decreases gastric emptying by 67%
- Native ghrelin has potent pro-motility effects on the rat model of POMI
- These effects are partially restored by several GHS1a receptor agonists
- These effects are fully restored by RM-131 at 100 fold greater potency native ghrelin
  - RM-131 also has the unique ability to induce supra-physiologic increases in gastric emptying

Implications

- RM-131 is a promising candidate for the treatment of both gastric and intestinal dysmotility disorders
  - phase 1 clinical trials are in progress
- The mechanism of action of the supraphysiologic effects of RM-131 are not known
  - ? regulated by a putative second ghrelin receptor
  - ? allosteric effects of RM-131 on GHS1a
- The strong effects of RM-131 on GI motility (despite its design optimization for weight gain) demonstrates that this compound is a broad spectrum ghrelin super-agonist, which suggests potential additional activity for cachexia and inflammatory disorders

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