Poster
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Oral Delivery of a GLP-1 Agonist with High Bioavailability in Dogs and Humans

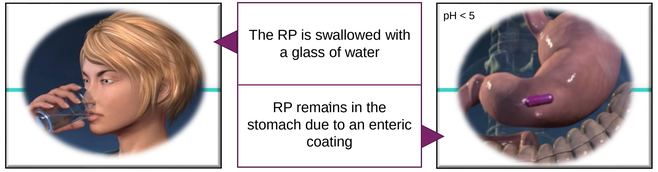
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INTRODUCTION AND STUDY RATIONALE

GLP-1 mimetics, which are highly efficacious as antidiabetic agents, are also proving to be effective for weight loss. While most require injections due to poor oral bioavailability, Rybelsus® (semaglutide) is orally effective for glycemic control, however, its 1% bioavailability and high dose requirement limits its viability as an effective oral weight-loss medication. Here, we demonstrate high oral bioavailability of the GLP-1 agonist, exenatide, A) in canines using an orally ingestible robotic pill (RP; RT-104) which painlessly injects drug transenterically in the proximal small bowel and B) in humans using an endoscopically guided transenteric injection which mimics RP delivery.

HOW THE ROBOTIC PILL WORKS

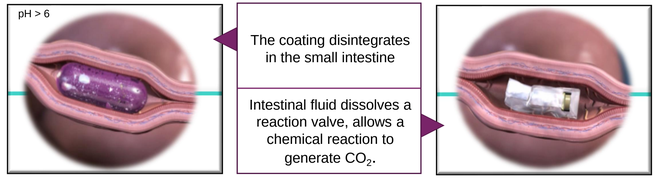
1. Enteric-coated Robotic Pill is Ingested



The RP is swallowed with a glass of water

RP remains in the stomach due to an enteric coating

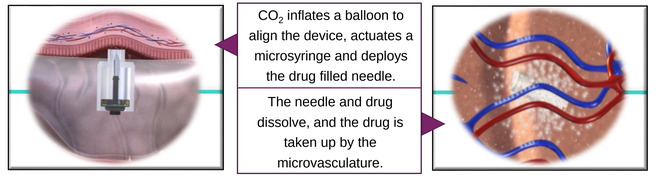
2. Enteric Coating Disintegrates in Small Intestine



The coating disintegrates in the small intestine

Intestinal fluid dissolves a reaction valve, allows a chemical reaction to generate CO_2.

3. Drug is Delivered



CO_2 inflates a balloon to align the device, actuates a microsyringe and deploys the drug filled needle.

The needle and drug dissolve, and the drug is taken up by the microvasculature.

MATERIALS AND METHODS

Oral RP Study in the Canine Model

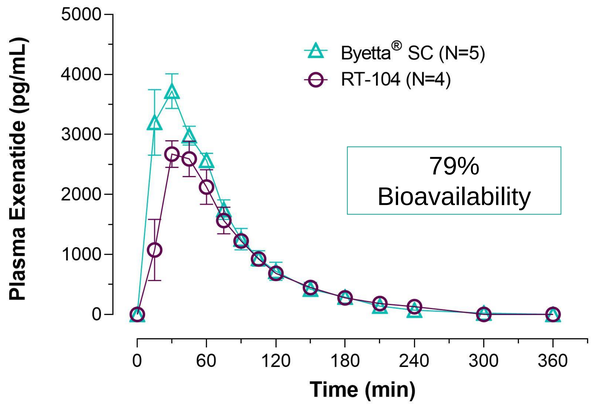
- 9 awake, fasted beagles weighing 8.0 - 11.0 kg received 10 µg exenatide via either subcutaneous (SC) injection or Robotic Pill (RT-104).
- The transit of RT-104 was monitored through the GI tract via fluoroscopy to confirm its successful passage and deployment in the small intestine.
- Serial blood samples were collected for up to 6 hours to measure plasma concentrations of exenatide via validated ELISA method.

Endoscopic Injection Study in Humans

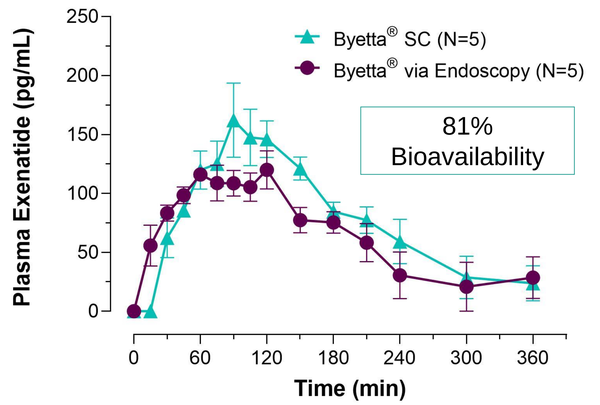
- Single-center, open-label, crossover study enrolled 3 healthy women and 2 healthy men between the ages of 18-30 years with BMI between 20 – 30 kg/m^2.
- All subjects first received 10 ug of exenatide via SC injection.
- After a wash-out period of 15 days, all subjects were lightly anesthetized and received 10 ug of exenatide via injection into the jejunal wall via endoscopically guided procedure.
- Serial blood samples were collected for up to 6 hours after each dose to measure plasma concentrations of exenatide via validated ELISA method.

PHARMACOKINETIC PROFILES

Canine PK Data



Human PK Data



PHARMACOKINETIC PARAMETERS

CANINE	C_{max} (pg/mL)	T_{max} (min)	AUC (ng*min/mL)
Byetta® SC (N=5)	3987 ± 276	27 ± 6	293 ± 14
RT-104 (N=4)	2800 ± 247	37 ± 4	231 ± 19

HUMAN	C_{max} (pg/mL)	T_{max} (min)	AUC (ng*min/mL)
Byetta® SC (N=5)	184 ± 24	96 ± 11	27 ± 3
Byetta® via Endoscopy (N=5)	139 ± 6	90 ± 13	22 ± 3

SUMMARY & CONCLUSIONS

- In both dogs and humans, the PK profiles of exenatide/Byetta delivered via the RP/transenteric route were similar to their respective SC control groups.
  - Bioavailability was found to be **79%** and **81%** of SC drug exposures in canines and humans, respectively.
- These data provide the basis for the clinical development of an orally ingestible GLP-1 mimetic (RT-104) which would provide the higher, efficacious exposures needed for both weight loss and glycemic control.

Visit www.ranitherapeutics.com to learn more
or scan the QR code to see a video of the Robotic Pill in action.