ORALLY-ADMINISTERED USTEKINUMAB BIOSIMILAR DELIVERED VIA A ROBOTIC PILL YIELDS BIOAVAILABILITY COMPARABLE TO SUBCUTANEOUS INJECTION IN CANINES

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Background & Purpose

- Ustekinumab offers an effective treatment for chronic inflammatory conditions like IBD but requires long-term injections that represent a burden for patients, interfering with their quality of life and therapeutic compliance. Patients overwhelmingly prefer oral dosing to injections. An effective oral alternative could improve patient compliance and encourage earlier adoption of proven therapies.
- We have developed an orally ingestible robotic pill (RP) that delivers biotherapeutic agents with bioavailability rivaling that of subcutaneous (SC) injections. In this study, we 1) provide pharmacokinetic (PK) model-based evidence that alternative ustekinumab doses achieve targeted therapeutic serum levels, and 2) demonstrate equivalent bioavailability of low dose and high dose ustekinumab delivered orally via RP relative to subcutaneous (SC) injections in canines.

Methods

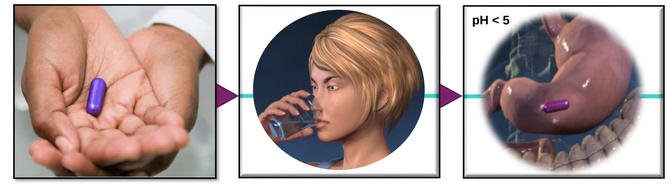
- Based on published human PK data, PK simulations were constructed for various daily dosing regimens targeting steady-state therapeutic serum concentrations using R 4.1.1 software.
- RPs containing ustekinumab biosimilar were orally administered to Beagles at 0.50 or 0.75 mg (n=8 per group), while a control group (n=6) received a 0.50 mg dose via SC injection. The high dose group was 18 mg (n=7), while a control group (n=3) received an 18 mg dose via SC injection. Serial serum samples were collected up to 27 days to measure the concentrations of ustekinumab.

Nonclinical PK Parameters

Route	C_{max} (µg/mL)	T_{max} (day)	AUC (day.µg/mL)	Dose Normalized AUC ((day.µg/mL)/mg)	Relative Bioavailability
RP 0.75 mg (n = 7)	1.1 ± 0.1	2 ± 0	8.2 ± 0.6	11.0 ± 0.8	91%
RP 0.50 mg (n = 6)	0.8 ± 0.1	2 ± 0	5.6 ± 0.6	11.3 ± 1.2	94%
SC 0.50 mg (n = 5)	0.6 ± 0.1	3 ± 1	6.0 ± 0.7	12.0 ± 1.4	---

Note: All data is mean ± SEM. PK data from three animals (two 0.50 mg RP and one 0.50 mg SC) were eliminated from final PK calculations due to rapid appearance of neutralizing anti-drug antibodies, a phenomenon common to canines exposed to human monoclonal antibodies regardless of route.

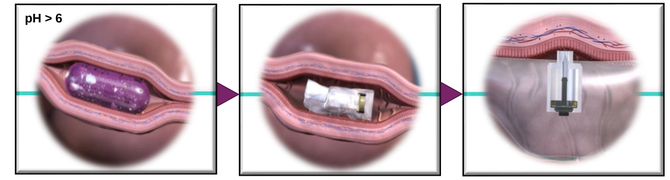
How the Robotic Pill Works



The RP is a pharmaceutical capsule about the size of a calcium pill.

The RP is swallowed with a glass of water.

The RP is protected by an enteric coating while in the stomach.



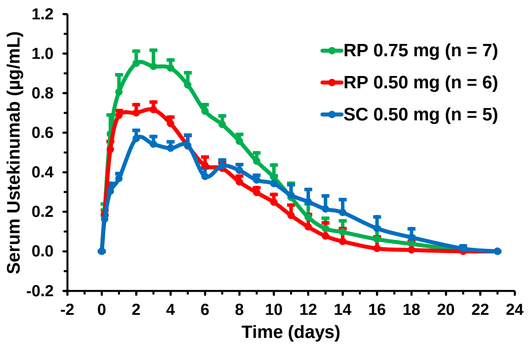
The coating disintegrates in the small intestine.

Intestinal fluid dissolves a valve starting an acid-base reaction.

CO_2 inflates a balloon to align the device and actuates a microsyringe.

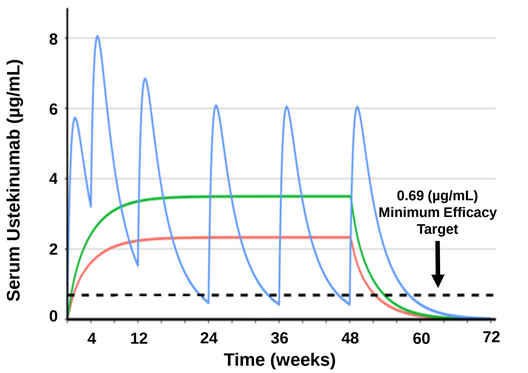
Results & Conclusions

Once Daily Oral Low Dose



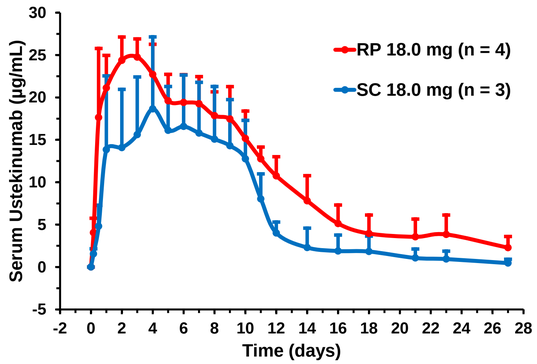
Oral ustekinumab (low dose) was successfully delivered in 15 of the 16 animal subjects.

The RP demonstrated >90% oral bioavailability of ustekinumab compared to SC injection, making oral dosing feasible.



Daily dosing of 0.75 mg (green) or 0.50 mg (red) ustekinumab may maintain steady state therapeutic serum concentrations more effectively than 45 mg every 12 weeks (blue).

Evaluation of a New High-Capacity RP



Route	C_{max} (µg/mL)	T_{max} (day)	AUC (day.µg/mL)	Relative Bioavailability
RP 18 mg (n = 4)	29.5 ± 4.7	2 ± 1	294 ± 39	159%
SC 18 mg (n = 3)	20.2 ± 8.0	5 ± 1	185 ± 56	---

Note: All data is mean ± SEM.

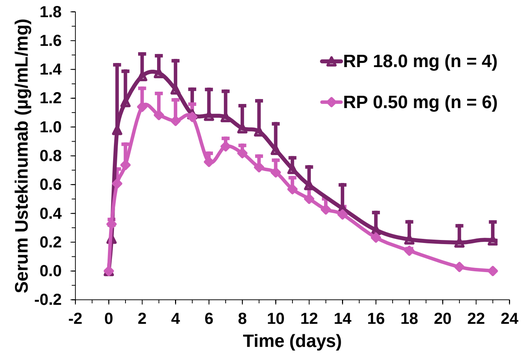
A new high-capacity RP (RP-HC) was evaluated in a small nonclinical trial in canines.

18 mg ustekinumab was successfully delivered orally using the RP-HC.

The RP-HC demonstrated >100% oral bioavailability of ustekinumab compared to SC injection but was likely skewed due to small sample size.

The RP-HC may allow maintenance of steady state therapeutic serum concentrations with less frequent oral dosing.

Dose normalized data suggest that ustekinumab has a signature PK profile, irrespective of the dose.



SCAN TO LEARN MORE

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All authors / presenters have a financial relationship with Rani Therapeutics including employee, officer or board member, ownership interest, intellectual property / patents, and/or stock options.