An Orally Administered Robotic Pill (RP) Reliably and Safely Delivers an Ustekinumab Biosimilar With High Bioavailability Relative to Subcutaneous (SC) Ustekinumab in Healthy Human Subjects

Jacques Van Dam, MD, PhD

Vice President, Medical Affairs
Rani Therapeutics, Inc.
San Jose, CA

Professor of Medicine
Keck School of Medicine
University of Southern California

Joshua Myers, Son Nguyen, Nidhi Patel, April Toledo Vo, Alyson Yamaguchi, Kyle Horlen, Baber Syed, Mir Imran, Mir A. Hashim, Arvinder K. Dhalla.

Rani Therapeutics, Inc. San Jose, CA

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DDW2024
Digestive Disease Week®
MAY 18-21, 2024 | WASHINGTON, D.C.
EXHIBIT DATES: MAY 19-21, 2024

DISCLOSURE INFORMATION

Jacques Van Dam, MD, PhD

I disclose the following financial relationship(s) with a commercial interest

- Rani Therapeutics, Inc. San Jose, CA

INTRODUCTION

- **Purpose**
  - To evaluate the pharmacokinetics (PK) of an ustekinumab biosimilar, administered via a robotic pill (RP) capsule to healthy volunteers.

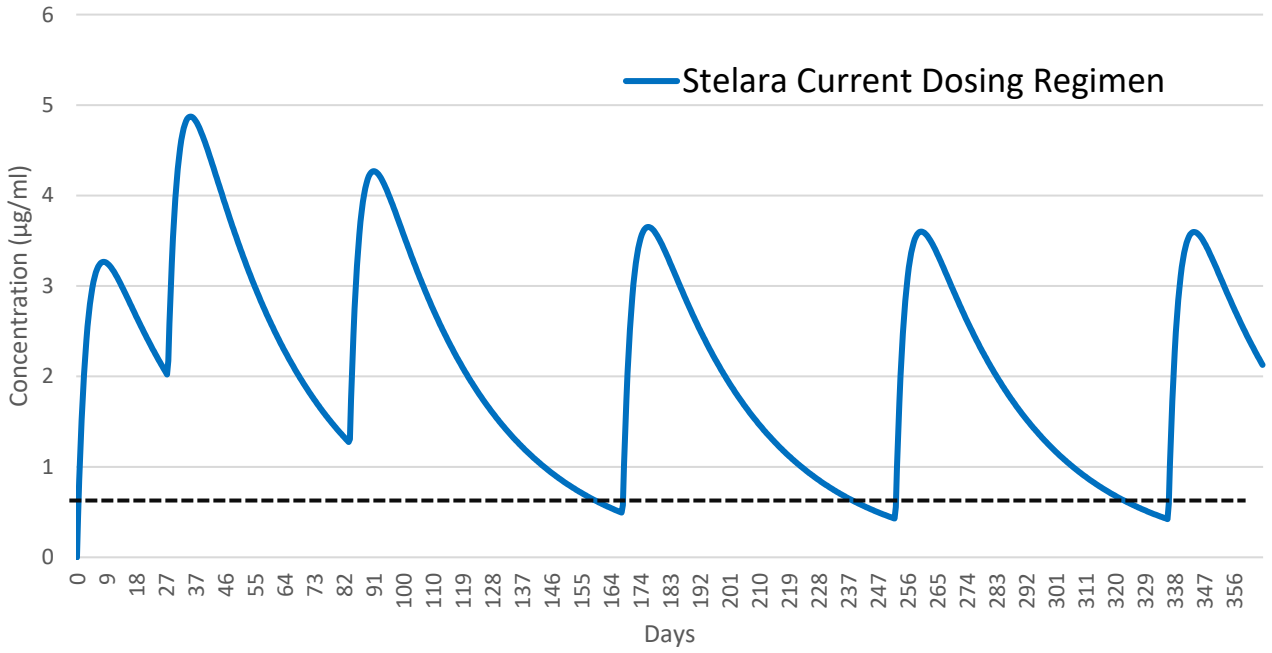
- **Ustekinumab**
  - A monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23 and has been approved for the treatment of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.
  - Ustekinumab (Stelara®) has been in clinical use for over a decade. Its typical dosing regimens are 45mg or 90mg administered via SC injection every 12 weeks.

INTRODUCTION: DRUG DELIVERY

- **Route of Administration**
  - Like all biologics, biosimilars, peptides, GLP-1, ustekinumab cannot be taken orally due to inactivation in the gastrointestinal tract. Ustekinumab is therefore delivered parenterally via subcutaneous (SC) injection.

- **Dosing Frequency**
  - Ustekinumab requires long-term injections that present 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.

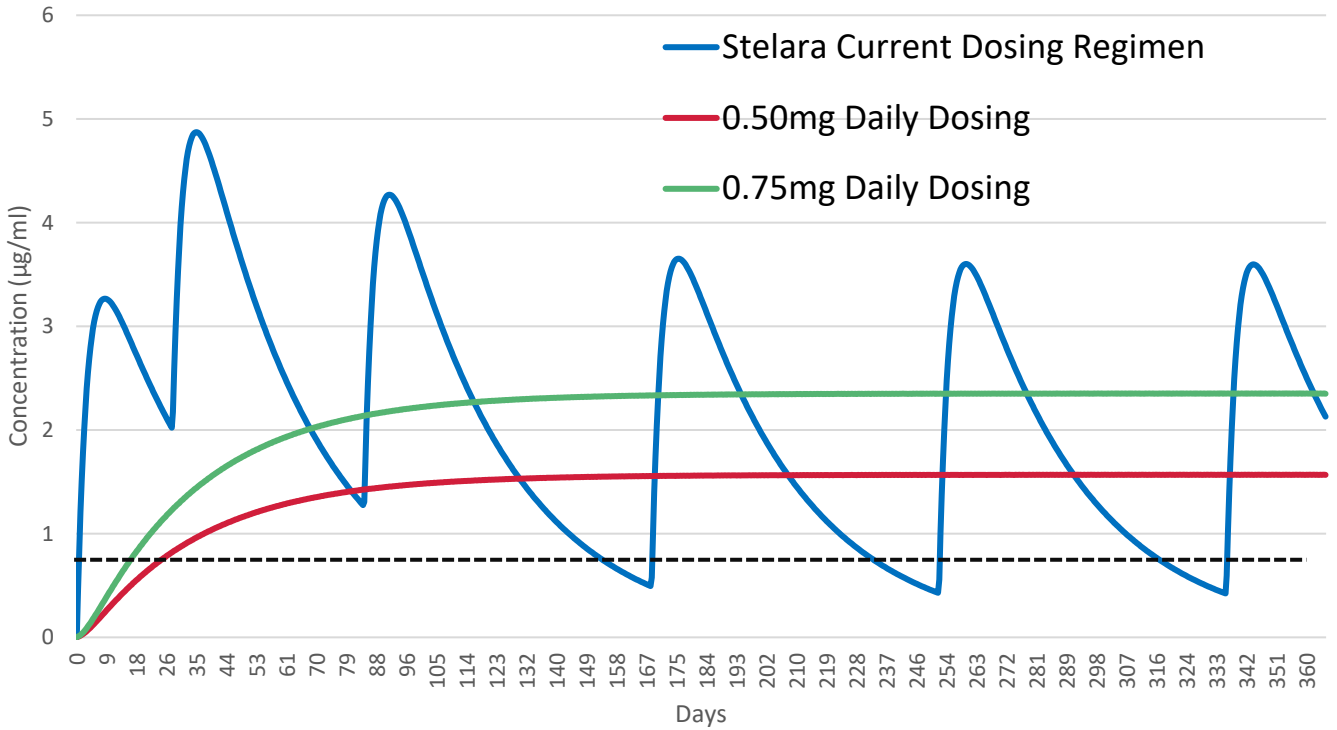
PK SIMULATIONS OF USTEKINUMAB (45 MG SC QUARTERLY)



Current dosing regimen of 45 mg every 12 weeks results in serum concentration below therapeutic levels around week 10-11

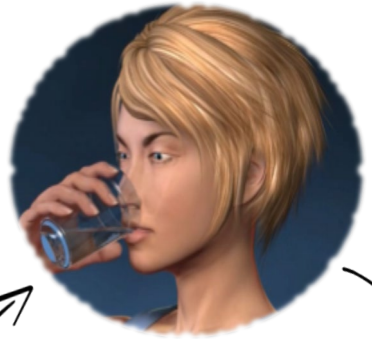
Target Therapeutic Concentration = 0.7 µg/ml

PK SIMULATIONS OF USTEKINUMAB (45 MG SC QUARTERLY VS. RP 0.5 AND 0.75 MG ORAL DAILY)

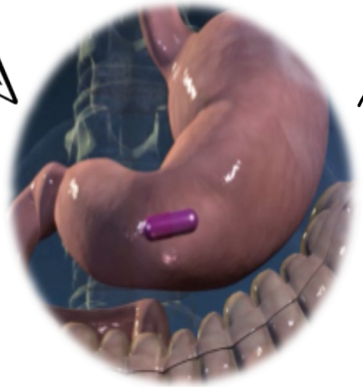


Daily dosing of 0.50 mg (red) or 0.75 mg (green) of ustekinumab in RP may maintain steady state serum concentrations more effectively than 45 mg every 12 weeks (blue)

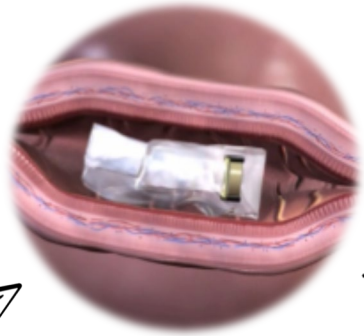
ROBOTIC PILL TECHNOLOGY



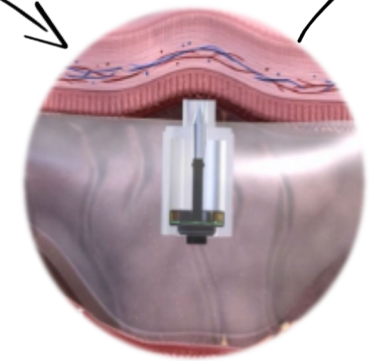
RP containing ustekinumab biosimilar



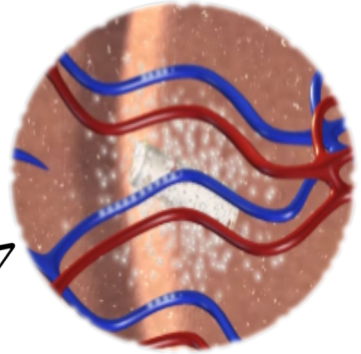
Enteric coating protects RP against gastric pH



Coating dissolves in intestinal pH, moisture enters the RP and triggers chemical reaction generating CO_2



Balloon inflates, needle is inserted through the intestinal wall, and payload is injected



Needle and drug payload dissolve, taken up by surrounding vasculature

PHASE 1 CLINICAL TRIAL: STUDY OVERVIEW

An Open Label, Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics (PK) of an Ustekinumab Biosimilar (CT-P43; Celltrion, Inc.) – Administered Orally via Robotic Pill to Healthy Volunteers

Objective	To assess safety, tolerability and PK of ustekinumab delivered orally via a robotic pill
Study Population	Healthy men and women volunteers recruited from the general population
Study Site	Single center
End Points	PK parameters, safety and tolerability

STUDY DESIGN

- Study Groups
  - Control Group: 0.50mg ustekinumab (Stelara) SC (N=15)
  - Group 1: 0.50mg ustekinumab biosimilar (CT-P43) in RP (N=20)
  - Group 2: 0.75mg ustekinumab biosimilar (CT-P43) in RP (N=20)

- Participants were given a single dose of the study drug (SC or PO) after an overnight fast

- Blood samples were collected at various time points over 60 days and analyzed for ustekinumab concentrations

STUDY DEMOGRAPHICS

	SC (0.50 mg)	Group 1 (0.50 mg)	Group 2 (0.75 mg)
N	15	20	20
Mean Age, years (Range)	29.3 (19 - 49)	28.3 (20 - 39)	30 (20 - 58)
Race			
Hispanic	0% (0/15)	25% (5/20)	5% (1/20)
White-non-Hispanic	60% (9/15)	35% (7/20)	75% (15/20)
Asian	40% (6/15)	35% (7/20)	20% (4/20)
Russian	0% (0/15)	5% (1/20)	0% (0/20)
Body Mass Index (kg/m^2) (Mean ± SD)	23.8 ± 3.4	25.5 ± 3.7	22.9 ± 2.2

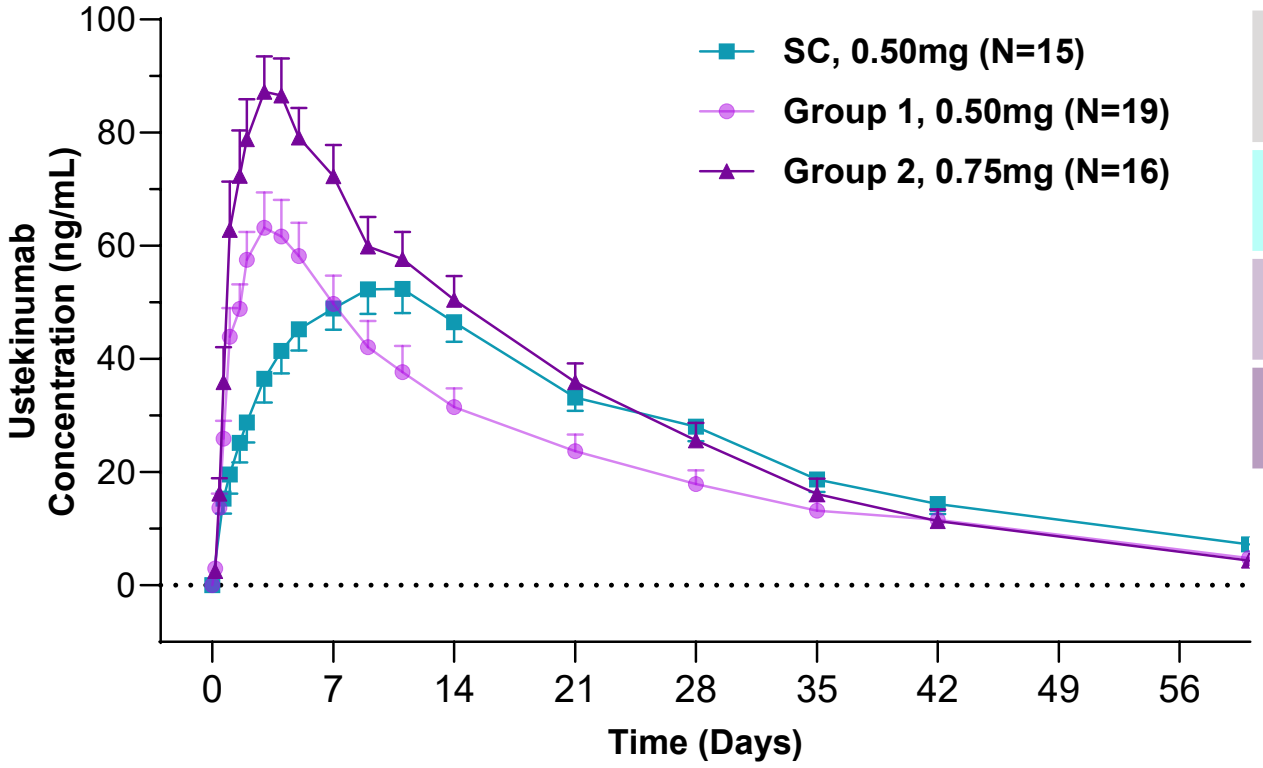
ROBOTIC PILL PERFORMANCE: SUBJECT TOLERANCE

Participant Questionnaire (N=40)

1. Did you have any difficulty swallowing the RaniPill?
2. Describe your experience with the swallowability of the pill?
3. How does the pill taste?
4. How easy was the pill to swallow?
5. Immediately upon administration to the mouth, how does the pill surface feel on the tongue?
6. Does the pill stick to the roof of your mouth?
7. Did you experience any unusual sensations after swallowing the RaniPill?
   - 7.1 Describe type of sensation?
8. Did you experience any pain after swallowing the RaniPill?
   - 8.1 Indicate location where you felt pain.

- RP success rate = 88%
- 100% Participants able to swallow RP
- 98% (39/40) Participants had no difficulty swallowing the RP
- 100% (40/40) Participants reported no pain after swallowing the RP

PHARMACOKINETICS: MEAN PK PROFILES USTEKINUMAB SC VS. ORAL RP (CT-P43)



Pharmacokinetic Parameters

Group	C_{max} (ng/mL)	T_{max} (days)	AUC_{0-t} (day.ng/mL)
SC 0.50mg (N=15)	56 ± 4	10 ± 0.8	1,566 ± 130
Group 1: 0.50mg (N=19)	67 ± 7	3.1 ± 0.2	1,315 ± 150
Group 2: 0.75mg (N=16)	92 ± 8	3.3 ± 0.2	1,814 ± 165

Estimated Bioavailability Relative to SC **84%**

Estimated bioavailability based on 0.5mg dose

INCIDENCE OF ADVERSE EVENTS

	Adverse Events	SC, 0.50 mg (N=15)	Group 1, 0.50 mg (N=20)	Group 2, 0.75 mg (N=20)
	All	1	2	0
Drug-Related	Abdominal Bloating	0	1 (5%)	0
	Injection Site Rash/Reaction	1 (6.7%)	0	0
RP-Related	Burning Sensation in stomach*	N/A	1 (5%)	0

*Burning sensation in stomach perceived 1 hour after capsule administration and lasted for 30 minutes. However, drug levels were not seen for 10 hours after capsule administration indicating that the capsule had not deployed at time of the reported pain which suggests that this AE is not related to the drug or RaniPill deployment. However, presence of the undeployed capsule in the stomach could have causality to the reported pain.

SUMMARY

SAFE

Ustekinumab biosimilar delivered via RP was well-tolerated
No SAEs

EFFECTIVE

Ustekinumab biosimilar delivered via RP demonstrated HIGH bioavailability

FUTURE DIRECTION

Successful use of the RP to deliver monoclonal antibodies demonstrates the potential for this oral route of delivery