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RESEARCH

Oral delivery of an ustekinumab biosimilar with bioavailability comparable to subcutaneous administration in healthy human participants

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Abstract

Purpose Ustekinumab, targeting interleukin (IL)-12 and IL-23, is effective in treating chronic immune-mediated inflammatory diseases, but needs to be dosed via subcutaneous (SC) injection, which impacts patient comfort and treatment adherence. To enable oral dosing of ustekinumab, the utility of a robotic pill (RP) was evaluated in humans.

Methods A Phase 1 study was conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of single doses (0.5 and 0.75 mg) of an ustekinumab biosimilar (CT-P43) delivered via RP (RT-111) in healthy participants compared to ustekinumab (0.5 mg) administered via SC injection.

Results RT-111 was well-tolerated with no reported SAEs. Ustekinumab was detected in 35/40 participants dosed with RT-111. At the 0.5 mg dose, RT-111 and SC administration yielded similar C_{max} (RT-111: 67 ± 7 ng/mL, SC: 56 ± 4 ng/mL), while a dose-proportional increase in C_{max} was observed at the 0.75 mg dose (92 ± 8 ng/mL). Uptake via oral delivery was faster, with a T_{max} of 3 vs. 10 days for the SC group. Bioavailability of RT-111 was comparable (81%) to that of SC injection.

Conclusion This is the first report of successful oral delivery of a therapeutic antibody via an orally ingestible RP in humans, with bioavailability comparable to SC injection.

Clinical trial number Study was registered at Clinicaltrials.gov as NCT05890118 in May 2023.

Keywords Oral antibody delivery · Biotherapeutics · Robotic pill · Ustekinumab · Monoclonal antibody

Introduction

Translation of medical advances into targeted treatments has led to the development of biologic therapies, which offer high specificity and superior efficacy for many chronic conditions. In particular, biologics that target specific pro-inflammatory cytokines have been life-changing for individuals with chronic immune-mediated inflammatory diseases (IMIDs) like psoriasis. However, due to the size, nature, and structure of biologics, these macromolecules cannot overcome barriers in the gastrointestinal (GI) tract, and therefore can only be administered via parenteral injections. One such molecule is the human IgG1K monoclonal antibody, ustekinumab, which is an effective biologic treatment for individuals with moderate-to-severe psoriasis approved for nearly two decades [1–3].

Ustekinumab, like other biologic drugs, must be administered by injection due to its rapid degradation and inactivation in the GI tract [4]. For individuals who are initiating this therapy, the process of performing self-injections can be daunting [5]. Indeed, patients with chronic IMIDs are burdened with repeated administration of injections that interfere with quality of life, can stigmatize, and can elicit behavioral aversions and fear [6, 7]. Predictably, patients who inject biologics on a frequent basis overwhelmingly say they would prefer an oral alternative to their injectable

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drug [7–9]. Surprisingly, 50% of patients whose treatment regimen is more occasional (monthly or biannually) still prefer a pill over an injection, including individuals with moderate-to-severe psoriasis [10, 11]. More specifically, even though ustekinumab is administered via a subcutaneous (SC) injection every 3 months, patients would still prefer an oral ustekinumab option if it was available [11]. Furthermore, both patients and their physicians acknowledge that adherence with therapy would improve with the availability of orally delivered therapy [10, 11].

To address this unmet need for oral delivery of biologics [12, 13], an orally ingestible robotic pill (RP) has been developed that safely delivers biotherapeutics via transenteric injection directly into the small intestine [14–16]. The intestines are insensate to sharp stimuli and thus drug delivery via injection is not only painless, but also highly efficient for drug absorption [17, 18]. This oral RP has reliably delivered several biotherapeutics in porcine and canine models with bioavailability nearly identical to SC injections [14, 16, 19, 20]. Further, in human clinical trials, the RP delivered octreotide and teriparatide with high bioavailability and no serious adverse events (SAEs) in both single and repeated daily dosing [15, 21].

Preclinical studies showed that the RP was able to deliver an ustekinumab biosimilar (CT-P43) with bioavailability comparable to SC injections in canines [20]. To confirm these data in humans, a Phase 1 study was conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of the RP containing CT-P43 (RT-111) in healthy participants. The current report describes the results of this Phase 1 study assessing two doses (0.5 mg and 0.75 mg) of RT-111 compared to SC injections (0.5 mg) of commercially available ustekinumab.

Materials and methods

Study design

This study was a prospective, single-center, open label, Phase 1 study to evaluate the safety, tolerability, and PK of orally delivered RT-111 and compare these data to commercially available ustekinumab, delivered by SC injection. The study was conducted at a single site (Australia), after obtaining approval from the Alfred Hospital Ethics Committee (ethics approval #395/23). Written informed consent was obtained from all participants before being included in the study. The study was performed according to the approved protocol and the guidelines for Good Clinical Practice.

Study participants ($N=55$) were divided into three groups: Group 1 ($N=15$) received 0.5 mg of ustekinumab via a single abdominal SC injection, Group 2 ($N=20$) received a single 0.5 mg oral dose of RT-111, and Group 3 ($N=20$) received a single 0.75 mg oral dose of RT-111. Additional participants were enrolled in the RT-111 groups compared to SC group to account for the failure of drug delivery via RP, based on the historical success rate of 90%. Serial blood sampling was taken periodically for 60 days post-drug administration to evaluate PK and presence of anti-drug antibodies (ADAs).

Clinical trial materials

RT-111 consists of the RP containing CT-P43 and was manufactured by Rani Therapeutics (San Jose, CA, USA). The RP is a versatile drug delivery platform, based on a 000 (31 mm by 11 mm) size capsule, designed to orally deliver biologics that are currently given via SC, intramuscular, or intravenous injections. The enteric coating on the RP is designed to withstand the acidic environment of the stomach. Disintegration of the enteric coating and capsule shell in the small intestine activates the underlying mechanism to actuate the RP whereby the drug is injected transenterically and rapidly absorbed. RP remnants are safely excreted with regular bowel movements. Details of the RP design, operation, reliability and safety have previously been reported [14, 15].

CT-P43 developed by Celltrion (Yeonsu-gu, Incheon, Republic of Korea) is approved in the European Union, Canada, Australia, and the United States. The CT-P43 drug solution was obtained from Celltrion and was lyophilized into a powder that was compacted into microtablets containing 0.5 mg or 0.75 mg of ustekinumab, inserted and sealed inside the dissolvable needles, and enclosed into the needle chamber under aseptic conditions to maintain sterility. All other components of the RP were assembled in a controlled environment. The sterility of the drug needles was tested and verified by an external CRO (Aemtek Laboratories, Fremont, CA).

Commercially available ustekinumab was purchased and provided to the clinical site for use in the SC injection control group. The drug solution was diluted to be administered at a dose of 0.5 mg/mL.

Study population

The study population consisted of fifty-five (55) male or female healthy participants, age 18 to 65, with a body mass index (BMI) of 19 to 32 kg m^{-2} who met all of the inclusion and none of the exclusion criteria. Subjects with known history of GI problems (including diverticulitis, stomach ulcers, inflammatory intestinal disease, gastrointestinal perforations/fistulae/intra-abdominal abscess, and abnormal/irregular

bowel movements) were excluded from the study. Subjects with a history of intolerance to ustekinumab, a known history of previous exposure to IL-12 and/or IL-23 inhibitors, history of prolonged immunosuppressant therapy or photochemotherapy treatment, or impaired liver function were also excluded. Also, subjects using proton pump inhibitors at doses higher than the lowest approved dose were excluded.

Study procedures

Participants were admitted to the clinical site the day before dosing and remained there through Day 4. Complete blood counts (CBCs), serum chemistry, and coagulation panels were completed on all participants at their screening visit and repeated on Day 6 and Day 61.

All participants fasted for at least 8 h but were allowed to have water during the fasting period. Water intake was restricted to no more than 250 mL (1 cup) up to 30 min prior to dosing in the RP groups. For Group 1 participants, ustekinumab was administered via a SC injection into the abdomen. Groups 2 and 3 were given RT-111 to be swallowed with 100 mL of water. Blood samples for PK analysis were collected prior to administration (pre-dose) and post-dose at 12, 24, 36, 48, 72, and 96 h for Group 1 and 4, 10, 16, 28, 40, 52, 76, and 100 h for Groups 2 and 3. The additional time points for blood sampling (4 and 10 h) and 4-hour delay for other time points for Groups 2 and 3 were included because the time of RP deployment was estimated to be ~4 h post-dose. During the outpatient period of the study, blood samples were collected on Days 5, 7, 9, 11, 14, 21, 28, 35, 42, and 60 in all groups for PK analysis and on Days 14 and 60 for ADA analysis.

In Groups 2 and 3, fluoroscopic imaging was conducted at five hours post-dosing on Day 1 to assess the deployment status of the RP. Participants were scanned again on each visit day until excretion of the RT-111 components was confirmed. Participants receiving RT-111 completed a detailed questionnaire about their experience of swallowing the capsule.

Safety assessments

To evaluate safety and tolerability of RT-111, adverse events were collected and sorted based on the type, incidence, timing, and severity to determine whether they were related to ustekinumab or the RP. All the participants who were dosed with RT-111 were included in the safety analysis even if they did not complete the study. Successful drug delivery was confirmed by measurement of drug levels in the blood and was used to confirm relatedness of adverse events to ustekinumab or RP.

Bioanalysis

Ustekinumab concentrations and qualitative determination of ADAs were measured in the serum samples using Meso Scale Discovery platform (Meso Scale Diagnostics, Rockville, MD, USA). For ustekinumab concentrations, this sensitive bridging electrochemiluminescent (ECL) assay used a ruthenium-labeled human anti-ustekinumab antibody. The lower limit of quantitation (LLOQ) for the assay was 1.95 ng/mL. The intra-assay and inter-assay bias (accuracy) and precision (CV) was <20%. Sample reanalysis was performed as recommended by the ICH M10 Guidelines. The repeat analysis data was comparable to the original values and within the prescribed criteria of ±30%. The ustekinumab concentrations assay validation and bioanalysis were performed by BioAgilytix (Durham, NC, USA).

For ADAs, the binding assay for screening, confirmatory, and titer determination was a bridging ECL assay utilizing a ruthenium-labeled ustekinumab for detection and human anti-ustekinumab antibody as positive control (PC) for the screening and confirmatory assays. For screening, the acceptance ranges of the high PC and low PC were 142.6–644.0 ng mL^{-1} and 1.4–3.2 ng mL^{-1}, respectively, with the intra-assay and inter-assay bias (accuracy) and precision (CV)<20%. The % inhibition for the confirmatory PCs was ≥23.2%. Titer determination was completed if the screening and confirmatory tests were reactive. The ADA analysis and assay validation was performed by Intertek (Manchester, UK).

Data analysis

Maximum serum concentration (C_{max}) and time to reach maximum concentration (T_{max}) were derived from the PK data. Area under the curve from 0 to 60 days (AUC_{0-60}) was determined using a standard non-compartmental method applying the trapezoidal rule on observed concentrations and the actual sampling time points. Bioavailability was calculated from AUC values as (AUC_{ORAL}/AUC_{SC})*100. MS Excel (version 2004 or later) and GraphPad Prism (version 9) were used for data analysis. Categorical data are expressed as counts and percentages, and continuous data as mean±standard deviation (SD) or standard error (SE), as indicated. Statistical analyses were performed using Prism v10.2 (GraphPad Software Inc.). T-test was done to compare PK parameters between two groups, while Fishers exact test was done for comparison of ADA incidence. Asterisks were used to denote significance; *$P<0.05$, **$P<0.01$, ***$P<0.001$.

Table 1 Demographic and baseline characteristics of study groups

	SC (0.5 mg)	RT-111 (0.5 mg)	RT-111 (0.75 mg)
N	15	20	20
Sex			
Male	60% (9/15)	55% (11/20)	40% (8/20)
Female	40% (6/15)	45% (9/20)	60% (12/20)
Age (years)			
Mean (Range)	29.3 (19-49)	28.3 (20-39)	30 (20-58)
Race % (n/N)			
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)
Other	0% (0/15)	5% (1/20)	0% (0/20)
BMI (kg m^{-2})			
Mean ± SD (Range)	23.8 ± 3.4 (19.1-29.4)	25.5 ± 3.7 (19.1-31.7)	22.9 ± 2.2 (19.3-26.4)
Range	(19.1–29.4)	(19.1–31.7)	(19.3–26.4)
Height (cm)			
Mean ± SD (Range)	172.7 ± 9.8 (156–189)	172 ± 9.7 (155–188)	170.2 ± 8.7(153–184)
Weight (kg)			
Mean ± SD (Range)	71.1 ± 12.7 (50.8–97.7)	76 ± 16.5 (46–108.5)	66.5 ± 9.5(50.6–83.7)

kg kilogram, *cm* centimeter, *mg* milligram, *BMI* body mass index

Table 2 Participant responses for swallowability of RT-111

Characteristic	% (*n*/*N*)
Did you have any difficulty swallowing the RaniPill	
Yes	2.5% (1/40)
No	97.5% (39/40)
Describe experience with swallowability of the pill	
Easy	72.5% (29/40)
Large Pill - Easy	22.5% (9/40)
Needs Extra Water	2.5% (1/40)
Somewhat Difficult	2.5% (1/40)
Pill Taste	
No Taste	97.5% (39/40)
Bad Taste	2.5% (1/40)
Ease of swallowing pill	
Easy	57.5% (23/40)
Somewhat easy	30% (12/40)
Neutral	10% (4/40)
Somewhat difficult	2.5% (1/40)
Feel of pill on tongue	
Smooth	35% (14/40)
Somewhat Smooth	22.5% (9/40)
Neutral	42.5% (17/40)
Stickiness of pill on roof of mouth	
Not Sticky	97.5% (39/40)
Sticks a Little	2.5% (1/40)
Unusual sensation while swallowing	
Yes	12.5% (5/40)[a]
No	88% (35/40)
Pain after swallowing	
No	100% (40/40)

[a]Burning sensation in stomach (1), itchiness behind left eyelid (1), popping sensation (1), hungry sensation (1), stomach grumbling (1)

Results

Participant characteristics

Out of the 55 subjects enrolled, 52 completed the study. Two participants were lost to follow-up post-dosing in the RT-111 0.75 mg group and one participant withdrew from the study for unknown reasons in the RT-111 0.5 mg group. Baseline demographics for participants were similar amongst the groups with no significant differences in age, BMI, height, or weight (Table 1).

RT-111 safety and tolerability

All participants were able to swallow RT-111. After swallowing, participants completed a questionnaire evaluating the ease of swallowing and texture/feel (smoothness or stickiness) of the capsule (Table 2). Participants (98%) reported they did not have any difficulty swallowing RT-111. Although 23% of the responses suggested that RT-111 was large, it was still considered easy to swallow in 95% of the responses. None of the participants reported any pain after swallowing RT-111.

Both doses of RT-111 were safe and well-tolerated with no SAEs observed in the study. There were four AEs reported related to either drug or RP which were either mild or moderate in severity, with none related to deployment of RT-111. In the SC group, there was one drug-related injection site reaction AE that resolved on its own. In the RT-111 0.5 mg group, there were two drug-related AEs; drug-related abdominal bloating ($N=1$) and transient burning sensation in the abdomen associated with an undeployed

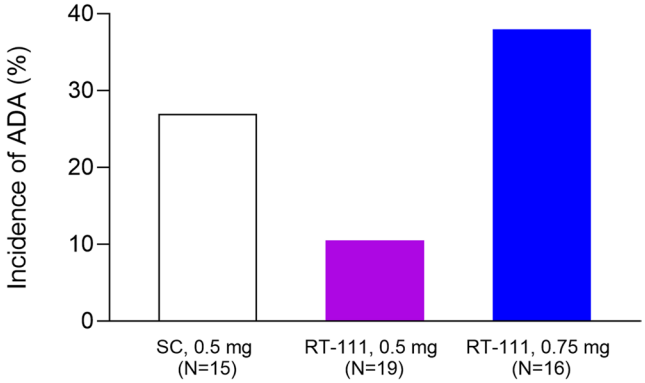


Fig. 1 Incidence of positive ADAs (anti-drug antibodies) (%) after a single dose of ustekinumab biosimilar (CT-P43) administered via SC injection (0.5 mg) or orally via RT-111 (0.5 or 0.75 mg) in healthy participants

RT-111 capsule in the stomach ($N=1$). The 'burning sensation' AE was perceived 1 h after capsule administration and lasted for 30 min. However, drug levels were not seen for 10 h after capsule administration indicating that the capsule had not deployed at the time of the reported pain, which suggests that this AE was not related to the drug or RP deployment. The presence of the undeployed capsule in the stomach could have causality to the reported pain. There were no AEs reported in the RT-111 0.75 mg group.

Three participants showed ADAs in the pre-dose samples whereas a total of 14 participants had ADAs at Day 61 post-dose. Titer levels were unchanged from pre-dose to post-dose in two of the participants suggesting RT-111 dosing did not result in new ADA formation. The incidence of development of ADAs in the RT-111 dose groups was 11% (0.5 mg, $N=2$) and 38% (0.75 mg, $N=6$), respectively while in the SC group (0.5 mg) 27% ($N=4$) of participants were positive or showed increasing titers for ADAs (Fig. 1).

Drug delivery by RT-111

Ustekinumab was detected in 19 out of 20 participants in the 0.5 mg group and 16 out of 20 participants in the 0.75 mg group. Imaging showed that a majority (36 out of 40) of RT-111 capsule deployments occurred within 5 h after dosing. Elimination of device remnants was confirmed by imaging by Day 3 in all ($N=40$) subjects, while in majority of the subjects ($N=23$) remnants were eliminated by Day 1.

RT-111 pharmacokinetics and bioavailability

The pharmacokinetics of ustekinumab were tracked for up to 60 days following administration of either oral RT-111 or ustekinumab SC injection (Fig. 2; Table 3). Absorption of ustekinumab was slower with SC injection with a mean T_{max} of 10 ± 0.8 days compared to 3 ± 0.2 days with RT-111. Peak serum concentrations (C_{max}) were similar between the RT-111 0.5 mg and the ustekinumab 0.5 mg SC groups. There was a dose-proportional increase in C_{max} in the RT-111 dose groups. PK profiles of the drug were not significantly different between males and females. Due to missing values, the AUC_{0-60d} was calculated from mean PK profiles for each group. The AUCs were similar in the three groups, with a bioavailability of 84% and 78% for the RT-111 0.5 mg and 0.75 mg groups, respectively, compared to SC (Fig. 2).

Discussion

Ustekinumab has been in clinical use for nearly two decades as a safe and effective treatment for chronic IMIDs like psoriasis [1–3]. Ustekinumab's current infrequent dosing

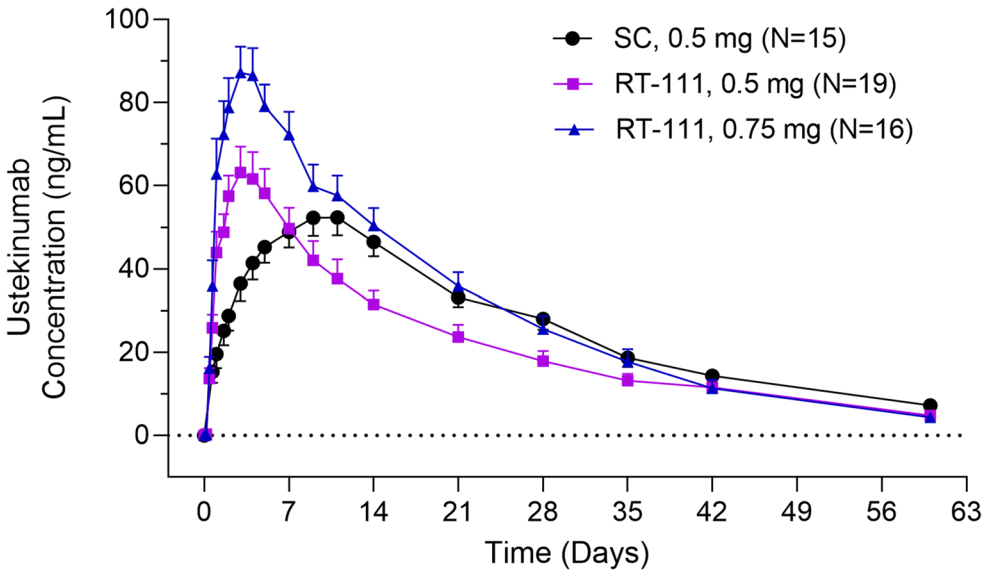


Fig. 2 Time-course of Mean ± SE changes in serum ustekinumab concentrations of healthy participants who received either a single 0.5 mg dose of ustekinumab via SC injection or single 0.5 or 0.75 mg doses of the ustekinumab biosimilar via oral administration (RT-111)

Table 3 PK parameters for ustekinumab administered via RT-111 and SC injection

Population	PK Parameters	SC 0.5 mg (*N* = 15)	RT-111 0.5 mg (*N* = 19)	RT-111 0.75 mg (*N* = 16)
All Participants	C_{max} (ng mL^{-1})	56 ± 4	67 ± 7	92 ± 8
	T_{max} (days)	10 ± 0.8***	3.1 ± 0.2	3.3 ± 0.2
	AUC (days*ng mL^{-1})	1566 ± 130	1315 ± 150	1814 ± 165
	Bioavailability	-	84%	78%
ADA Negative Participants Only		**SC 0.5 mg (N = 11)**	**RT-111 0.5 mg (N = 17)**	**RT-111 0.75 mg (N = 10)**
	C_{max} (ng mL^{-1})	58 ± 6	67 ± 7	93 ± 12
	T_{max} (days)	10.2 ± 0.9***	3.2 ± 0.2	3.1 ± 0.4
	AUC (h*ng mL^{-1})	1677 ± 112	1365 ± 142	1883 ± 162
	Bioavailability	-	81%	78%

Data presented as mean ± SE. *ADA* Anti-drug antibodies, *** $P<0.001$ significantly different from RT-111 groups

schedule (every 8–12 weeks following initial induction) is highly favored by patients compared to more frequently dosed drugs [22, 23]. But even with a 2–3 month dosing interval for ustekinumab, adherence with therapy has been shown to be as low as 57% [24, 25] and most patients would prefer oral therapy over injectables, if available and as effective as injectables [10, 11]. Until now, oral delivery of a monoclonal antibody such as ustekinumab has been elusive. Data from this study show oral delivery of a monoclonal antibody with high bioavailability in humans for the first time. RT-111 was safe, well-tolerated, and delivered the ustekinumab biosimilar with bioavailability comparable to SC injection. Based on the data from the current study and PK modeling, a once-daily oral regimen offering advantages over standard-of-care treatments (e.g., improvements in treatment consistency, therapeutic responsiveness, and overall patient experience) is possible.

Participants had no difficulty swallowing the RP, as reported previously [11, 15, 21] and there were no SAEs reported in the study. Two adverse events related to the RP were reported, which resolved without intervention. One participant reported a burning sensation while the RP was in the stomach; this resolved on its own and was determined to be unrelated to RP deployment, which occurred much later as confirmed by the presence of drug in the blood. Capsule deployment was verified by fluoroscopy in 36/40 participants and ustekinumab was detected in serum samples of 35/40 participants, resulting in a reliability rate of 88%. These data align with our previous studies that used RP for biotherapeutic drug delivery [15, 21]. A verified deployment not yielding detectable serum levels of ustekinumab could have resulted from misalignment of the needle relative to the mucosal wall due to GI tract anatomy (not a uniformly smooth surface) or a manufacturing defect of the RP. None of the participants reported any pain upon RP deployment, consistent with the fact that intestines are insensitive to sharp stimuli [17].

When comparing the development of new or increasing ADAs, the RT-111 0.5 mg group showed an incidence of 11% (2 participants), while the SC 0.5 mg group had an incidence of 27% (4 participants). Although the study is not sufficiently powered, or designed to evaluate ADA development, the observation of a lower incidence of new/increasing ADAs in the RT-111 0.5 mg group compared to the SC 0.5 mg group suggests that the transenteric route utilized by RT-111 may not be associated with an inherently higher risk of inducing ADAs.

RT-111 and SC ustekinumab both administered at 0.5 mg yielded similar PK profiles with equivalent C_{max} values. RT-111 yielded a dose-dependent increase in C_{max} at the 0.75 mg dose. Additionally, the C_{max} of RT-111 0.5 mg was proportional to the values reported for the clinical dose (45 mg) of ustekinumab (Stelara® Product Insert), suggesting that absorption of the drug delivered via RT-111 was similar to that of SC. The bioavailability (calculated from AUC) for ustekinumab with RT-111 0.5 mg was 84% relative to SC injection at the same dose. Absorption of ustekinumab was faster with oral RT-111 dosing compared to SC ustekinumab, with a mean T_{max} of ~3 days and ~10 days, respectively. As expected, pharmacokinetics of ustekinumab biosimilar were not different between males and females in all groups. PK parameters for the 0.5 mg SC group are comparable to published data for a single dose of SC ustekinumab in healthy participants [26].

The results observed in this study are consistent with previously generated canine data utilizing RT-111, which illustrated similar C_{max} values between RP and SC groups and slightly shorter T_{max} values for the RP group compared to SC administration [20]. Similar correlations between canine and human data have also been shown with a GLP-1 agonist [19], which further validates the canine model to be a predictive of pharmacokinetics generated in humans. While direct comparison of absolute PK values between species requires careful consideration due to inherent physiological differences, the relative performance and efficiency of the RP demonstrates consistency across varying biotherapeutics. This suggests that the numerous therapeutics that have been incorporated into the RP and assessed in the canine model [16, 27] would yield similar data in humans.

Faster absorption of ustekinumab with RT-111 relative to SC may be due to more efficient drug uptake mechanisms

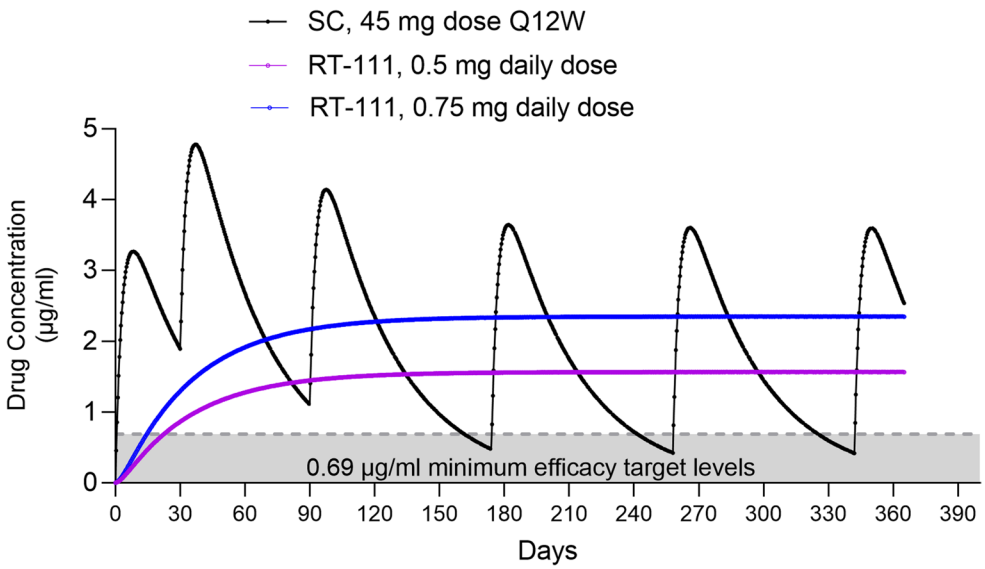


Fig. 3 PK simulations of different dosing regimens for ustekinumab. Black lines represent the currently approved quarterly SC dosing regimen whereas purple lines represent daily oral dosing via RT-111. The shaded area below represents the minimum drug levels needed for efficacy. Note that frequent (daily) dosing with low doses (0.5 mg and 0.75 mg) achieves smoother steady state therapeutic serum concentrations always above trough levels than infrequent (once every quarter) dosing with large (45 mg) doses. PK simulations were done using the PK parameters of Ustekinumab from Clinical Pharmacology Review section of Stelara BLA (# 125, 261/Supplement 150) from the FDA site (https://www.fda.gov/media/143135/download)

via intraperitoneal route of delivery. Large molecules such as antibodies cannot enter the systemic circulation via blood capillaries but rather rely upon uptake into lymphatic vessels [28–31]. Adipose tissue in the skin lacks lymphatic vessels, which could act as a drug sink and delay systemic absorption [30]. In a porcine model, T_{max} was significantly longer when ustekinumab was injected into deeper regions of the inguinal skin compared to more superficial areas [32]. In contrast, the peritoneal cavity is replete with lymphatic vessels for drug absorption [33, 34]. Thus, passage of drug into the intraperitoneal space (IP) would be rapidly absorbed by visceral lymphatic capillaries as IP administration of pharmacological agents results in faster and more complete absorption compared to oral and SC routes due primarily to the large peritoneal surface area containing lymphatic vessels [27, 34]. This faster drug absorption, like that observed with the RT-111, can significantly contribute to improved patient outcomes, by faster attainment of therapeutic concentrations resulting in earlier onset of clinical efficacy. This is particularly crucial when rapid symptom relief is paramount. Furthermore, consistent and predictable absorption profiles can reduce inter-patient variability in drug exposure, leading to more reliable therapeutic responses and optimized dosing strategies.

Ustekinumab has been commercially available since 2009 for the treatment of moderate-to-severe plaque psoriasis as well as active psoriatic arthritis, Crohn's Disease, and ulcerative colitis. Ustekinumab is administered as a SC injection at a dose of 45–90 mg initially followed by 45–90 mg doses every 12 weeks [26]. While therapeutic levels of ustekinumab for psoriasis were initially suggested to be around 0.7 µg mL^{-1}, higher steady state levels have been shown to be more efficacious [35, 36]. The very high SC doses given every 12 weeks yield serum levels as high as 10–12 µg mL^{-1}, but drug concentrations fall below therapeutic levels towards the end of the 12-week dosing interval (Fig. 3). This is the case with many other drugs that use infrequent injections of large doses such as adalimumab and dupilumab. For ustekinumab, these fluctuations lead to periods of subtherapeutic exposure toward the end of dosing intervals (Fig. 3), which can result in loss of response over time [35, 36]. This may be one of the reasons for lower efficacy of ustekinumab compared to other drugs [37–39]. The infrequent dosing schedule understandably considers patient convenience and preference for fewer and less frequent injections. However, oral dosing utilizing the RP can be done daily and, although more frequent, would still be preferred by the majority of current ustekinumab users [11]. This has not been possible until now because ustekinumab (or any biologic) cannot be taken orally.

RT-111 was designed to orally deliver a small dose of ustekinumab that, when taken daily, can result in sustained drug levels well-above required therapeutic levels (Fig. 3). Daily oral dosing allows for more stable and predictable drug levels by maintaining drug concentration levels within the therapeutic window. Data presented here demonstrate that the oral RP can safely and effectively deliver

ustekinumab. PK simulations show that daily oral dosing at 0.5 mg or 0.75 mg would maintain steady state concentrations of ustekinumab between 2 and 4 μg mL^{-1} and avoid the large peaks and troughs in serum drug levels seen with the large doses of ustekinumab injected every 12 weeks (Fig. 3). Stable serum levels may also translate to a more reliable pharmacodynamic response. Furthermore, a daily oral regimen may allow for a more precise titration of dose depending on patient response or tolerability compared to biologics dosed over long intervals. In this regard, a newer version of the RP with higher capacity is currently being developed that will be more amenable for titration of drugs at higher levels.

While this study clearly demonstrates that RP can successfully deliver large antibodies such as ustekinumab, the study does not verify that intestinal drug delivery evokes a therapeutic response. This could not be evaluated in this study because a single low dose of the drug used in the study was not sufficient to show an effect. However, lower doses were used in this study to obtain PK of the drug via RP in humans at doses that would allow for daily dosing. Dose-response observed with the two doses of RT-111 suggest that higher doses may also be delivered just as effectively with the new version of the RP, which could result in less frequent dosing (e.g., weekly), further enhancing patient convenience.

In conclusion, oral delivery of an ustekinumab biosimilar via RT-111 was safe, with bioavailability comparable to SC injection in humans. A daily oral pill offers an appealing alternative to current injectable antibodies, like ustekinumab, by providing a stable therapeutic exposure that may minimize adverse effects and improve clinical outcomes. The long-term safety and efficacy of RT-111 remains to be determined in future studies. These early phase data suggests that a daily orally delivered antibody has the potential to reshape the management of chronic IMIDs.

Author contributions Conceptualization: AKD, MAH, MI, JTM. Investigation: JVD, OG. Methodology: MI, ATV, LCF, AY, DM. Data Curation: LCF, AY, KH, AD, MH, JTM. Formal Data Analysis and interpretation: JTM, AKD, MH, MAH, AB. Writing - Original Draft Preparation: JTM, AD, MAH. Writing - Review and Editing: JTM, AD, MAH, KH, JVD, AY, ATV, AB.

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Data availability The datasets generated during and/or analyzed for the current study are available from the corresponding author on request.

Declarations

Human ethics and consent to participate declaration This study was carried out in accordance with the ethical standards and protocols approved by the local ethics committee. Written informed consent was obtained from all participants before being included in the study.

Principal investigator statement The authors confirm that the Principal Investigator for this paper is Ofer M. Gonen, MD, PhD, FRACP and had direct clinical responsibility for patients.

Competing interests All authors, except Ofer Gonen and Andrew Blauvelt, were employees of the company at the time the work was conducted. Dr. Blauvelt has served as a speaker (received honoraria) for Eli Lilly and Company, UCB, and Almirall, has served as a scientific adviser (received honoraria) for AbbVie, Almirall, Alumis, Amgen, Anaptysbio, Apogee, Arcutis, Astria, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Corvus, Dermavant, Eli Lilly and Company, Galderma, GlaxoSmithKline, Immunovant, Incyte, IQVIA, Janssen, Leo, Lipidio, Merck, Novartis, Oruka, Paragon, Pfizer, Rani Therapeutics, Regeneron, Sanofi, Spherix Global Insights, Sun Pharma, Syncona, Takeda, UCB, Union, and Zai Lab, has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Almirall, Alumis, Amgen, Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Eli Lilly and Company, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, Takeda, and UCB, and owns stock in Lipidio and Oruka.

What is already known about this subject Therapeutic antibodies, such as ustekinumab, cannot be taken orally due to rapid degradation by digestive enzymes. Formulation strategies, such as encapsulation and targeted delivery, are under development to overcome these barriers to oral delivery of antibodies.

What this study adds This study shows that a novel, orally ingestible robotic pill (RP) can protect an antibody from digestion and auto-deploy in the small intestine, delivering the biologic as a painless transenteric injection with high reliability and bioavailability, similar to a subcutaneous (SC) injection. PK simulations project that a more frequent (oral) dosing regimen will maintain steady state therapeutic exposures within a narrow range, potentially minimizing adverse effects and improving therapeutic outcomes, unlike the high peak-to-trough variability in circulating drug levels typically observed with typical SC injection dosing intervals.

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