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ORIGINAL ARTICLE

An oral robotic pill reliably and safely delivers teriparatide with high bioavailability in healthy volunteers: A phase 1 study

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Aims: The incidence of osteoporosis is projected to exceed 70 million people over the age of 65 years by 2030. Osteoanabolic agents, such as teriparatide and abaloparatide, are not only effective in reducing fracture incidence but also improve skeletal microstructure—an important need not met by antiresorptive agents. However, anabolic agents must be administered by daily subcutaneous injections which can be a challenge in older women. To address this need, we have developed an oral robotic pill (RP) designed to deliver biotherapeutics safely and painlessly.

Methods: This report describes the results of a 2-part Phase 1 study conducted to evaluate the safety, tolerability and pharmacokinetics of single (Part 1) and repeat doses (Part 2) of teriparatide delivered via the RP (RT-102) in healthy and postmenopausal women.

Results: Teriparatide, administered by the RP, was measurable in 26/29 and 63/69 of participants in Part 1 and Part 2, respectively. RT-102 at the 20-μg dose yielded a lower maximum observed serum concentration (98 ± 10 *vs.* 128 ± 20 pg mL^{-1}), delayed time to reach maximum observed serum concentration (68 ± 15 *vs.* 13 ± 2 min) and higher area under the curve to infinity (342 ± 44 *vs.* 126 ± 29 h pg mL^{-1}) resulting in a 3-fold higher bioavailability than subcutaneous injection. RT-102 was well tolerated with only 5 mild to moderate adverse events (AEs) related to the RP that resolved without intervention and no serious AEs. Drug-related AEs were similar in severity and frequency between RT-102 and subcutaneous teriparatide.

Conclusion: These data demonstrate that RT-102 can safely and reliably deliver therapeutic levels of teriparatide.

Clinicaltrials.gov: NCT#05164614.

KEYWORDS
biotherapeutic, osteoporosis, parathyroid hormone, oral drug delivery, robotic pill, teriparatide

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

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1 | INTRODUCTION

Osteoporosis is a debilitating disease characterized by loss of bone mass and architectural deterioration resulting in increased incidence of fractures and pain. As a result, the disease is associated with higher morbidity, mortality, disability and reduced quality of life.[1] The total annual cost for care, both medical and societal, was estimated at $57 billion in 2018, with an expected increase to over $95 billion by 2040.[2] Thus, improved treatment options for osteoporosis to reduce fractures are essential to address the impact of osteoporosis in an aging population.

Osteoanabolic agents represent an important therapeutic option for the treatment of osteoporosis because they primarily stimulate bone growth. These agents include peptide mimetics of human parathyroid hormone (PTH) such as **teriparatide** (PTH[1–34]),[3,4] which has been in clinical use for several decades as a safe and effective therapy. Another more recently approved peptide, **abaloparatide**, has similar effects.[5–7] While highly effective, these agents need to be injected daily for years and are thus not widely used due to the pain, inconvenience, fear of needles and/or negative impressions of drugs that must be injected.[8–11] While adherence rates for patients prescribed teriparatide vary widely, rates at 1 year can fall to levels as low as 10%.[12] For example, compliance was 35% at 12 months in a Japanese study[13] and 57% for Medicare patients in the USA.[14] A recent survey found that patients and prescribing physicians prefer a once daily pill, if available, over biotherapeutics administered via injection for chronic conditions.[15]

To address this unmet need for an oral anabolic therapy for osteoporosis, we have developed a versatile, oral robotic pill (RP) designed to deliver a variety of biotherapeutics transenterically across the small intestine into the intraperitoneal (IP) space.[16,17] The RP is a mechanical device enclosed in a standard capsule shell that is enteric coated to keep it protected in the acidic environment of the stomach. Once the RP reaches the small intestine, the change in pH dissolves the enteric coating and capsule shell, exposing a balloon that becomes an autoinjector. Inside the ballon is microsyringe that contains a precise dose of the biotherapeutic packaged inside a dissolvable needle. Exposure to intestinal fluid triggers a chemical reaction that leads to rapid inflation of the balloon, allowing the microsyringe to align perpendicularly to the long axis of the small intestine and inject the dissolvable needle carrying the drug into the intestinal wall. Drug delivery by RP is painless because the intestine is insensate to stimuli such as piercing or cutting.[18]

Previously, we have shown that several biotherapeutic drugs can be safely and reliably delivered via the RP with bioavailability comparable to or rivalling that of subcutaneous (SC) injections in nonclinical[16,19–22] and clinical studies.[17] The goal of the present study was to evaluate the safety and reliability of the RP to deliver teriparatide. The current report describes the results of a Phase 1 study assessing the safety and pharmacokinetics (PK) of single and repeat doses of teriparatide delivered by the RP compared to SC injections of commercially available teriparatide.

What is already known about this subject

- Major therapeutic approaches for osteoporosis aim primarily at stopping bone loss rather than building bone, because anabolic agents need to be administered via daily subcutaneous injections and in general are more expensive.
- Instead of a daily injectable, several attempts have been made to administer teriparatide using different modes of delivery.

What this study adds

- This study shows that a novel, oral robotic pill can deliver teriparatide with high reliability and bioavailability.
- Repeat dosing of RT-102 for 7 days delivered teriparatide with high reliability and was safe and well tolerated.

2 | METHODS

2.1 | Description of the robotic pill

The RP is a mechanical drug delivery system enclosed within an enteric coated 000-capsule (11 mm diameter and 32 mm length, which is similar in size to a fish oil or calcium pill) developed to deliver biologics orally. The RP is designed to withstand the acidic environment of the stomach and pass into the small intestine intact. Exposure to the higher pH within the small intestine allows the enteric coating and capsule shell to disintegrate, thereby initiating a series of events in which a folded balloon inside inflates and aligns a drug carrying microsyringe perpendicularly to the intestinal wall. Once sufficient pressure is reached within the balloon, a dissolvable needle containing the drug is delivered transenterically into the peritoneal space. The RP remnants left in the intestinal lumen are excreted with regular bowel movements. Details of the RP design, operation, reliability and safety have been reported previously.[17]

2.2 | Test materials

The RP containing teriparatide (RT-102) was manufactured by Rani Therapeutics. Teriparatide was procured from Bachem (Switzerland) and lyophilized with excipients (polyethylene glycol, mannitol and acetic acid) under GMP conditions at the University of Iowa Pharmaceuticals. The lyophilized powder was compacted into microtablets containing 20 or 80 μg of teriparatide, inserted and sealed inside the dissolvable needles. The sterility of the drug needles was tested and verified (Aemtek Laboratories, Fremont, CA, USA).

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For the comparator group, commercial teriparatide was obtained in a single-patient-use prefilled pen injector containing 28 daily doses of 20 μg each for injection.

2.3 | Study design

This study was a prospective, single-centre, open label, Phase 1 investigation to evaluate the safety and PK of orally delivered RT-102 and to compare these data to teriparatide delivered by SC injection. The study was approved by the Alfred Hospital Ethics Committee (ethics approval #13/22). The study had 2 components: Part 1 compared the PK of single doses of RT-102 and teriparatide in healthy volunteers; Part 2 evaluated the safety and reliability of repeat administration of RT-102 in healthy volunteers and postmenopausal women.

To evaluate safety and tolerability of RT-102, adverse events (AEs) were recorded and categorized by type, incidence, timing and severity to consider whether they were related to teriparatide or the RP. All dosed participants were included in the safety analysis even if they did not complete the study. The time of RT-102 deployment was confirmed by fluoroscopic imaging. Successful drug delivery was confirmed by measurement of drug levels in the blood and was used to describe a potential relationship of AEs to teriparatide or RP.

Two doses of teriparatide in RT-102 capsules, 20 and 80 μg, were evaluated in the study. The 20 μg dose was selected to do a direct comparison with the 20 μg SC dose which is the approved dose for teriparatide. The 80 μg dose was evaluated to do an indirect comparison with abaloparatide, which is approved as a SC injection at 80 μg.

2.4 | Study population

Women with a known history of gastrointestinal (GI) diagnoses (e.g., history of chronic constipation, gastroparesis/delayed gastric emptying, gastric or duodenal ulcers, dysphagia, dyspepsia, oesophagitis, oesophageal spasm, gastroesophageal reflux disease, inflammatory bowel disease, Crohn's disease, stomas, tumours, ischaemic or ulcerative colitis) or using a higher than the lowest approved therapeutic dose regimen of proton-pump inhibitors were excluded. Also excluded were women with a history of intolerance to PTH(1–34), osteoporosis, other bone disorders, Cushing's disease, abnormality in parathyroid hormone function or malabsorption syndromes identified within the past year. Women currently being treated with PTH, PTH-related peptide-derived drugs, anabolic steroids or bisphosphonates within the past year were excluded. All participants were not menstruating (to avoid confusion between menstrual pain/cramps and abdominal pain potentially due to RP), not pregnant and not lactating with a body mass index of 19–32 kg m^{-2}.

Part 1: The study population consisted of 40 healthy volunteers, aged 18–65 years. Study participants were divided into 3 groups: Group 1 ($n = 15$) received a single 20μg dose of RT-102; Group 2 ($n = 15$) received a single 80 μg dose of RT-102; and Group 3 ($n = 10$) received 20 μg teriparatide via a single abdominal SC injection. Part 2: The study population consisted of both healthy volunteers aged 18–65 years ($n = 5$) and postmenopausal women ($n = 5$) who received a daily 20 μg dose of RT-102 for 7 days.

2.5 | Study procedures

2.5.1 | Part 1

Participants remained at the clinical site overnight before dosing and for PK sampling. Complete blood counts and serum chemistry panels were completed at screening and following PK sample collections. Participants remained in the clinical unit up to Day 2 and returned daily for outpatient visits until the pill remnants were confirmed to have been eliminated.

All participants fasted for at least 10 h and abstained from liquids for at least 1 h prior to dosing. For Group 3, teriparatide was injected into the abdomen. Blood samples were collected predose and at 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 90, 120, 150, 180, 240, 300 and 360 min postdose for PK analysis. Similarly, in Group 1 and Group 2, a predose blood sample was collected before swallowing RT-102. Capsule transit through the GI tract was monitored by periodic fluoroscopy. While the capsule was in the stomach, an image was taken every 30 min to measure gastric emptying time (GET). Once the capsule reached the small intestine, an image was taken every 20 min until the deployment (dispersion of barium sulfate powder) to measure intestinal deployment time. The time of confirmed RP deployment via imaging was marked as T = 0 and PK samples were collected at the same intervals as Group 3. Food was offered to participants 7 h after RT-102 administration. Participants with GET >7 h or an intestinal deployment time >5 h were excluded for logistical reasons and replaced to maintain the sample size.

Subsequently, participants in Groups 1 and 2 were periodically scanned until excretion of RT-102 remnants was confirmed.

2.5.2 | Part 2

Participants were admitted to the clinical unit to receive a once-a-day, 7-day course of RT-102 20 μg capsules. Participants fasted for at least 8 h and consumed no liquids for at least 1 h prior to dosing on Days 1–6. Food was provided 3 h after dosing and food consumption was unregulated for the remainder of each day. Blood samples were collected on Days 1–6 predose and at 180, 360 and 540 min postdose.

As this was the first repeat dose study with RP in humans, out of an abundance of caution, the total number of intact capsules or capsule remnants were restricted to no more than 5 total or 2 located in the same area of the GI tract on any given day. Dosing was stopped

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in participants exceeding these limits, and they were discharged from the study after confirming all RP remnants were excreted.

On Day 7, after a fasting period of at least 10 h, a predose blood sample was collected, RT-102 administered, then blood samples were collected at 15, 30, 60, 90, 120, 240, 360, 480, 720 and 960 min following fluoroscopic verification of deployment in the small intestine. Food was offered to participants 7 h after RT-102 administration. Participants who completed the repeat dosing procedures remained in the clinical unit up to Day 8. Imaging was performed at follow-up visits, as necessary, to confirm RT-102 remnant excretion.

All RT-102 participants completed a questionnaire evaluating the ease of swallowing and texture/feel of the capsule.

2.6 | Teriparatide serum bioanalysis

Teriparatide levels were determined in serum samples using a validated high sensitivity enzyme-linked immunosorbent assay (Quidel Corp. OH, USA). The assay primarily detects human PTH(1–34) and has <3% cross reactivity with PTH(1–84). Calibration standards and controls containing teriparatide in serum matrix were used following the kit manual. The lower limit of quantitation for the assay was 15 pg mL^{-1}. The intra-assay and interassay bias (accuracy) and precision (coefficient of variance) was <20%. Sample reanalysis was performed as recommended by the ICH M10 Guidelines. The repeat analysis data were comparable to the original values and within the prescribed criteria of ±30%.

2.7 | PK parameters and analysis

All participants whose blood samples showed serum concentrations above lower limit of quantitation were included in the PK analysis. PK parameters for teriparatide were calculated using noncompartmental analysis with R version 4.2.1 (R package, pkr version 0.1.3) using actual blood sampling time. The parameters analysed included maximum observed serum concentration (C_{max}), time to reach C_{max} (T_{max}), $T_{1/2}$, total oral clearance (CL/F) and apparent volume of distribution (Vd/F), and area under the curve (AUC) *vs.* time from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$).

GraphPad Prism (version 9) and MS Excel (version 2004 or later) were used for data analysis. Categorical data are expressed as counts and percentages, and continuous data as mean ± standard deviation or standard error, as indicated.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[23,24]

3 | RESULTS

3.1 | Participants

In Part 1, 43 participants were enrolled in the study. Four participants were excluded from the study postdosing due to vomiting the intact capsule (1) or having GET ≥7 h (3). For Part 2, 17 participants were enrolled to receive repeat doses of RT-102, with 10 completing the study. Of the 17 eligible participants, 6 withdrew before completing the study due to: menstruation (2), reaching the capsule remnant number limit in the GI tract (2), unrelated elevation in eosinophils which resolved subsequently without intervention (1), and intravenous access difficulty (1). On Day 7, 1 participant was excluded due to GET being ≥7 h. However, all 17 participants received daily dosing repeatedly for at least 3 of the 7 days.

3.2 | Participant characteristics

Baseline demographics were similar among the groups with no significant differences in age, body mass index, height or weight (Table 1). Participants in Part 2 were split evenly between healthy volunteers and postmenopausal women (Table 1) with a mean age of 25.6 and 60 years, respectively.

3.3 | RT-102 swallowability

In total, 136 RT-102 capsules were administered (Part 1: $n = 32$; Part 2: $n = 104$) and all participants were able to swallow RT-102 (Table 2). Participants (93%) reported they did not have any difficulty swallowing the RP. Although ~25% of the responses suggested that RT-102 was large, it was still considered easy to swallow according to 90% of the responses.

3.4 | RT-102 safety and tolerability

Both doses of RT-102 were safe and well-tolerated with no serious AEs reported. In the RP groups, 5 drug related AEs (nausea, vomiting, constipation, diarrhoea, headache) and 5 RP-related AEs (bloated feeling, vomiting of the RP, abdominal pain [2], burping) were reported, which were mild or moderate and resolved without intervention. A total of 6 drug-related AEs were reported in the SC group (headache [1], light headedness [2], nausea [3]).

3.5 | Deployment time and reliability of drug delivery by RT-102

Fluoroscopic imaging was performed on participants to track the transit of RT-102 in the GI tract. The average time to deployment after

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TABLE 1 Demographic and baseline characteristics of study groups.

	Part 1			Part 2	
	RT-102 20 μg	RT-102 80 μg	SC 20 μg	RT-102 20 μg (HV)	RT-102 20 μg (PM)
N	15	14	10	5	5
Age (years)					
Mean	31.2	31.2	32.6	25.6	60
Range	(19–61)	(20–63)	(18–63)	(22–35)	(54–65)
Race % (*n*/*N*)					
Hispanic	7 (1/15)	0 (0/14)	10 (1/10)	20 (1/5)	0 (0/5)
White—non-Hispanic	80 (12/15)	79 (11/14)	50 (5/10)	20 (1/5)	100 (5/5)
Asian	7 (1/15)	7 (1/14)	20 (2/10)	40 (2/5)	0 (0/5)
Asian-Pacific Islander	0 (0/15)	14 (2/14)	20 (2/10)	20 (1/5)	0 (0/5)
Pacific Islander	7 (1/15)	0 (0/14)	0 (0/10)	0 (0/5)	0 (0/5)
BMI (kg m^{-2})					
Mean (SD)	23.5 ± 4	25.2 ± 4	23.6 ± 4	23.7 ± 2.5	25.3 ± 5
Range	(19.2–31.7)	(19.2–31.8)	(20–30.3)	(20.4–26.9)	(20.9–31.7)
Height (cm)					
Mean (SD)	164.3 ± 7	163.9 ± 6	162.5 ± 8	158.8 ± 6	159.8 ± 5
Range	(150–174)	(150–177)	(148–173)	(154–168)	(154–165)
Weight (kg)					
Mean (SD)	63.3 ± 11	67.5 ± 10	62.4 ± 12	60.6 ± 10	64.3 ± 10
Range	(45.4–84.5)	(52.6–85.6)	(48–79.9)	(50.2–76)	(55.6–75.4)

Abbreviations: BMI, body mass index; HV, healthy volunteer; PM, postmenopausal; SC, subcutaneous; SD, standard deviation.

ingestion of RT-102 was 208 ± 59 min ($n = 39$). The device remnants were excreted within 2.5 ± 1.2 days.

In Part 1, teriparatide was detected in 12 out of 15 participants in the 20 μg group and all 14 participants in the 80 μg group. In Part 2, out of the 70 RT-102 capsules administered to the 10 participants who completed the study, 69 were confirmed to have deployed by imaging. Teriparatide was detected in 63 of the 69 deployed capsules at ≤180 (33), 181–360 (28) and ≥540 (2) min post-RT-102 administration. (Table 3).

Data from all 17 participants for Days 1–6 of dosing showed that there were 72 deployments with successful drug delivery. Out of the 72, 35 deployments occurred during the first 180 min postdose when participants were in the fasted state and the remaining 37 deployments occurred within 6 h after food was consumed. Given that an equal number of capsules resulted in successful drug delivery in fasted and fed state, this result suggests that the presence of food did not affect device performance or the drug delivery.

3.6 | RT-102 PK and bioavailability

In Part 1, the PK of teriparatide were obtained following single doses of RT-102 and teriparatide SC (Figure 1 and Table 4). In the SC group, teriparatide was near or at C_{max} in the first serum sample measured and the average (±standard error) C_{max} was 128 ± 20 pg mL^{-1}. Levels declined steadily in the SC group for the next 120 min and were undetectable in 50% of participants within 90 min and in all participants at 240 min. The T_{max} of RT-102 at 20 μg was longer (68 ± 15 min) compared to the SC group (13 ± 2 min), suggesting that absorption of teriparatide was slower with RT-102. C_{max} was similar between SC and RT-102 groups at 20 μg dose of teriparatide. Compared to the SC administration of teriparatide, RT-102 exhibited a longer half-life ($T_{1/2}$: SC 33 ± 3 min; RT-102 107 ± 12 min) and yielded a 2.7-fold higher estimated bioavailability based on $AUC_{0\text{-inf}}$ ($AUC_{0\text{-inf}}$: SC 126 ± 29 h pg mL^{-1}; RT-102 20 μg 342 ± 44 h pg mL^{-1}), consistent with high clearance and volume of distribution for the SC route compared to RT-102. There was a disproportionate increase in serum teriparatide concentrations with the 80 μg dose of RT-102 relative to 20 μg RT-102 or SC, reaching a C_{max} of 971 ± 221 pg mL^{-1}, thus resulting in $AUC_{0\text{-inf}}$ that was 5-fold higher compared with the SC group ($AUC_{0\text{-inf}}$: SC 126 ± 29 h pg mL^{-1}; RT-102 80 μg 2600 ± 693 h pg mL^{-1}) consistent with low clearance and volume of distribution (Table 4). The T_{max} for the 80 μg dose was 60 ± 9 min and similar to the 20 μg dose of RT-102 indicating similar rate of drug absorption.

The PK curve of teriparatide obtained on Day 7 after repeated daily dosing (Part 2) is also shown in Figure 1. The PK sampling duration in Part 2 was extended to 12 h after the deployment of RT-102 to accurately determine the time of drug elimination. Drug levels were detected in all participants, but complete PK profiles were obtained in

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TABLE 2 Participant responses after swallowing RT-102.

Characteristic	Part 1 % (*n*/*N*)	Part 2 % (*n*/*N*)
Did you have any difficulty swallowing the RaniPill?		
Yes	7% (2/29)	7% (7/102)
No	93% (27/29)	93% (95/102)
Describe experience with swallowability of the pill		
Easy	66% (19/29)	66% (67/102)
Large pill—easy	24% (7/29)	27% (28/102)
Challenging due to size	7% (2/29)	1% (1/102)
No comment	3% (1/29)	6% (6/102)
Pill Taste:		
No Taste	100% (29/29)	100% (102/102)
Ease of swallowing pill:		
Easy	59% (17/29)	50% (51/102)
Somewhat easy	24% (7/29)	25% (26/102)
Neutral	10% (3/29)	22% (22/102)
Somewhat difficult	7% (2/29)	3% (3/102)
Feel of pill on tongue:		
Smooth	59% (17/29)	60% (61/102)
Somewhat smooth	24% (7/29)	7% (7/102)
Neutral	14% (4/29)	28% (29/102)
Somewhat rough	3% (1/29)	4% (4/102)
Rough	0% (0/29)	1.0% (1/102)
Stickiness of pill on roof of mouth:		
Not sticky	90% (26/29)	94% (96/102)
Sticks a little	10% (3/29)	6% (6/102)
Pain after swallowing:		
Yes	3% (1/29)	4% (4/102)
No	97% (28/29)	96% (98/102)

8 of the 10 participants on Day 7. No drug was detected in predose samples indicating no accumulation of the drug with repeat dosing, although C_{max} (296 ± 86 pg mL^{-1}) and $AUC_{0\text{-}inf}$ (876 ± 133 h pg mL^{-1}) with repeated dosing in Part 2 were greater than that of a single dose of RT-102 in Part 1. T_{max} was similar in the 2 parts indicating similar rate of absorption. Drug levels were not detected in any of the samples at the 12-h timepoint, again suggesting that the drug was eliminated by that time.

4 | DISCUSSION

This study demonstrates the safety and tolerability of oral RT-102 capsules resulting in the successful delivery of teriparatide with high bioavailability relative to SC injections in humans. Teriparatide has been in clinical use for >2 decades as a safe and effective osteoanabolic agent for osteoporosis.[4,25–27] However, teriparatide requires daily SC injections, which can reduce patient adherence and persistence with therapy, resulting in suboptimal outcomes.[12–14] Patients overwhelmingly prefer oral therapies over injectables, and physicians report that patient compliance and persistence would improve with availability of oral dosing alternatives.[15]

4.1 | RT-102 safety and tolerability

Data from the current study demonstrate that RT-102 was easy and safe to swallow with no serious AEs. A total of 5 AEs related to the RP were reported and resolved without intervention. Most of the participants did not experience any pain upon device deployment; however, in the repeat dose portion there were 2 reports of mild, transient abdominal pain occurring within the first 3 days of repeat dosing which may be related to the RP deployment (e.g., release of CO_2 gas).[18] The reported AE was mild and not present after Day 3, suggesting that the participant may have become acclimated to that sensation. There were 5 mild drug-related AEs which were similar to those reported with teriparatide SC, such as bloating, nausea and vomiting. Importantly, there were no AEs associated with daily administration of RT-102 for 7 days, and all capsule remnants were verified via imaging to have been successfully excreted without incident. This is the first demonstration that the RP can safely and repeatedly deliver medication in humans.

4.2 | RT-102 reliability of drug delivery

RT-102 delivered teriparatide with high reliability following single and repeated daily dosing of teriparatide via RP. Only the participants who completed the study were counted in the determination of reliability rate. Out of the total 136 RT-102 capsules administered, 98 were verified to have deployed (29 in Part 1 and 69 in Part 2), and teriparatide was detected in serum samples of 89 (26 in Part 1 and 63 in Part 2), yielding a drug delivery success rate of 91%. The small number of verified deployments that did not yield detectable serum levels of teriparatide probably resulted from misalignment of the needle relative to the mucosal wall (not a uniformly smooth surface) or a manufacturing defect. These data show that daily dosing of RP could result in occasional missed doses; however, in the case of teriparatide, that may have little or no impact on the efficacy given that weekly or biweekly administration of the same or larger doses of PTH is as effective as daily administration of teriparatide for bone building.[28–34] In this regard, weekly dosing with 56.5 μg teriparatide[28,32–34] or twice weekly dosing with 28.2 μg teriparatide[29,30] were safe and equally effective at improving bone mineral density (BMD) and reducing fracture risk in postmenopausal osteoporosis patients. Thus, intermittent dosing by RT-102 with an occasional missed dose is expected to be at least as effective as daily SC dosing.

Drug delivery with RT-102 did not seem to be affected by food intake. In the repeat-dose portion of the study, 49% of successful deployments occurred before food consumption, while 51% occurred after food intake. There was no correlation between failures and the timing of food consumption. These data are in line with a previous

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TABLE 3 Timing of detection of drug signal post daily administration of RT-102 for 7 days.

	Time to drug detection (min)						
Participant ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7[a]
112	360	360	360	180	180	180	230
113	ND	360	360	360	360	360	280
120	180	180	180	360	180	360	185
130	ND[b]	180	180	ND	180	ND	175
137	180	360	180	180	180	180	155
138	360	180	360	360	180	360	182
139	180	180	180	180	360	180	186
141	360	ND	>540	180	360	180	358
148	ND	540	180	180	180	180	302
149	180	ND	360	180	180	360	211

Abbreviation: ND, no drug detected.

[a]Exact time of deployment was determined by imaging and not estimated as on Days 1–6.

[b]Capsule deployment could not be verified—this capsule is not included in the total number of capsules confirmed deployed.

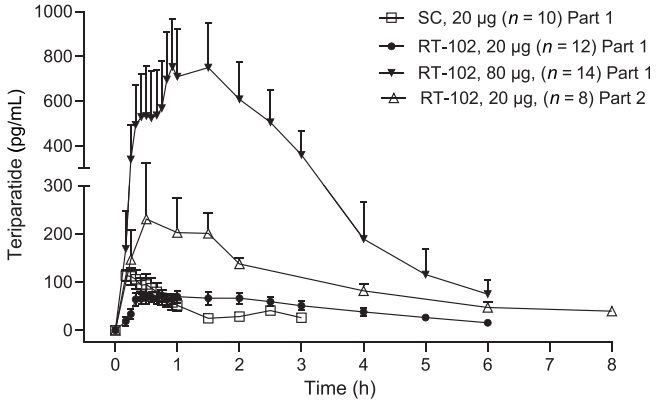


FIGURE 1 Mean ± standard error serum concentration–time profiles of teriparatide delivered as a single dose either via subcutaneous (SC) injection (teriparatide 20 µg) or orally (RT-102 at 20 and 80 µg doses) and after repeat doses of RT-102 at 20 µg dose in female volunteers.

study showing that food consumption does not affect RP deployment.[17] This suggests that the RP has an advantage over other chemistry-based oral formulations in that food restriction may not be required. While chemistry-based oral formulations require patients to restrict food intake for several hours before or after taking medications,[35–37] these findings suggest the RP may be an advantageous oral alternative in that food restriction may not be required.

4.3 | RT-102 PK and bioavailability

RT-102 and SC administration of teriparatide yielded similar C_{max}, however, RT-102 exhibited a longer $T_{1/2}$ resulting in bioavailability 3–4 times greater than SC teriparatide suggesting oral delivery with direct access to the small intestine may yield better results than SC injection. The results show that both AUC and C_{max} were increasing disproportionally with respect to dose. This is consistent with published data and is a known feature of teriparatide PK.[38]

The PK profile of RT-102 yielded a slower T_{max} and slower elimination resulting in much higher AUC compared to SC. Longer T_{max} observed with RT-102, compared to SC, may be due to a slower rate of absorption with the differences in drug formulation (solid *vs.* liquid) and route of injection. The complete elimination of teriparatide from the circulation following SC administration took about 4 h whereas with RT-102, serum levels were detected up to 6 h. The sustained peak with RT-102 could potentially elicit superior osteoanabolic effects. In fact, the PK profile of RT-102 at 80 µg is similar to that of abaloparatide, a closely related analogue of teriparatide, which is dosed at 80 µg (Figure 2). While both teriparatide and abaloparatide reduce fracture risk, the latter with longer exposure has shown a greater increase in BMD in the lumbar spine, femoral neck and total hip region.[39] Evidence of a longer (6-h) stimulation time by PTH(1–34) being more optimal for bone formation at the cellular level was demonstrated by Ishizuya *et al.*, who showed the diverse effects of PTH on osteoblast differentiation and that formation of mineralized bone nodules are a function of exposure time.[40] Taken together, these data suggest that longer exposure to PTH, as seen with abaloparatide and RT-102, may result in enhanced bone building capacity as compared to SC teriparatide, which has a relatively shorter exposure time owing to its short (1 h) elimination half-life. The similarity of the PK profile of teriparatide with RT-102 at 80 µg to that of SC abaloparatide (Figure 2) suggests that RT-102 may demonstrate better efficacy at lower doses than SC teriparatide at 20 µg. The PK curve obtained on Day 7 in Part 2 was similar to that obtained in Part 1, albeit with a higher C_{max}, but is within the reported variability (70–200 ng mL^{-1}) for teriparatide across various studies.[41–43]

The superior bioavailability of teriparatide observed with RT-102 relative to SC is probably due to efficient drug uptake mechanisms via the IP route of drug delivery.[44] Typically, following SC administration, the drug can undergo some pre-systemic proteolysis in the interstitial

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TABLE 4 Pharmacokinetic parameters for teriparatide administered via RT-102 and subcutaneous (SC) injection.

	Part 1			Part 2
	Teriparatide SC 20 µg ($n = 10$)	RT-102 20 µg ($n = 12$)	RT-102 80 µg ($n = 14$)	RT-102 20 µg ($n = 8$)
C_{max} (pg mL^{-1})	128 ± 20	98 ± 10	971 ± 221	296 ± 86
T_{max} (min)	13 ± 2	68 ± 15	60 ± 9	57 ± 12
T_{max} (min), median (range)	10 (10–30)	48 (15–180)	50 (20–120)	46 (30–125)
$AUC_{0\text{-}inf}$ (h pg mL^{-1})	126 ± 29	342 ± 44	2600 ± 693	876 ± 133
$T_{1/2}$ (min)	33 ± 3	107 ± 12	98 ± 11	164 ± 33
CL/F (L h^{-1})	866 ± 143	264 ± 36	71 ± 18	104 ± 17
V_Z/F (L)	633 ± 83	602 ± 73	178 ± 49	349 ± 83

Note: Data presented as mean ± standard error.
Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; CL/F, apparent plasma clearance; T_{max}, time to maximum concentration; $T_{1/2}$, half-life; V_Z/F, apparent volume of distribution.

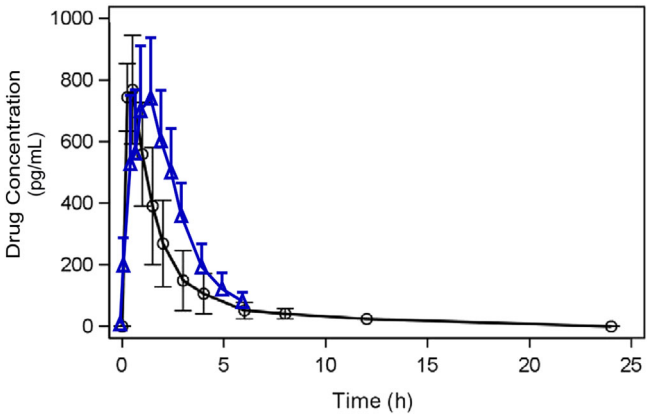


FIGURE 2 Mean ± standard error concentration–time profiles of serum concentrations of teriparatide delivered via RT-102 at 80 µg (blue triangles) superimposed on the concentration–time profiles of abaloparatide (open circles). Data reproduced from abaloparatide package insert.

tissues of the dermis which may account for some loss in systemic concentrations. Teriparatide, when delivered via SC injection, with a molecular weight of 4.1 kDa, is absorbed by capillaries of the dermis and rapidly degraded by nonspecific proteolysis in the liver, kidney and plasma. In contrast, it has been demonstrated that IP administration of pharmacological agents results in faster and more complete absorption resulting in higher AUC compared to oral and SC routes.[44] A unique aspect of transenteric/intraperitoneal drug delivery is access to a large surface area which leads to rapid and efficient absorption via visceral peritoneum, mesentery, omentum and the lymphatic system.[44,45] Thus, it is highly likely that some teriparatide was taken up into the lymphatics and released back into the systemic circulation slowly. The slow lymphatic system flow rate (0.2–2% of blood flow) coupled with lymph bypassing first pass degradation probably accounts for the longer half-life and increased bioavailability of teriparatide via RT-102. Additional studies are warranted to confirm these possibilities and to further understand the physiological mechanisms of this route of administration. Overall, the differences in PK profiles of teriparatide delivered via RT-102 and SC may be due to the difference in route of administration but also due to solid *vs.* liquid formulation. A newer version of the RP is in development that will deliver the payload in liquid form and will probably yield PK profiles closer to SC.

To date, the most effective osteoanabolic therapies are biologics that require an injection either daily (teriparatide 20 µg; abaloparatide 80 µg) or multiple injections monthly (romosozumab-aqqg, 2 105-mg doses). Teriparatide has been on the market for >2 decades with an excellent track record of safety and efficacy. Successful oral delivery of therapeutic levels of teriparatide by RT-102 in this study demonstrates that patients currently injecting these drugs daily could be provided an oral alternative. Furthermore, higher bioavailability of oral teriparatide compared to SC administration suggests lower daily dosing or reduced frequency of treatment may be viable options. This potential dosing paradigm change may result in improved patient adherence—an important factor in patients discontinuing treatment.[14] From a safety perspective, even though the current study evaluated only 7 days of repeat administrations of RT-102, our nonclinical data show that daily repeat administrations of RP for 60 days are safe and well tolerated (unpublished data). To get an early readout on efficacy, we conducted a study in the ovariectomized osteopenia rat model with direct intraperitoneal injections of teriparatide mimicking the RP route of delivery, which yielded robust, dose-dependent increases in BMD assessed by dual-energy X-ray absorptiometry and were comparable to SC controls.[46] These data demonstrate that the transenteric delivery of teriparatide is therapeutically viable.

5 | LIMITATIONS

While this study clearly demonstrates that RP can successfully deliver therapeutic levels of peptides such as teriparatide and abaloparatide, this study does not directly verify that intestinal drug delivery evokes a therapeutic response, such as an increase in bone density or bone turnover biomarkers. These parameters were not evaluated because a

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short treatment duration (7 days) would not be sufficient to show an effect on these parameters, especially in a small dataset of the study participants who were healthy and did not have osteoporosis.

6 | CONCLUSIONS

Despite the benefits of injectable teriparatide over antiresorptive therapies, its clinical uptake has been hampered by practical considerations, including the route of administration. Due to this limitation, many patients who could benefit from teriparatide treatment have instead selected oral antiresorptive therapies. RT-102 delivered teriparatide, orally, with high bioavailability and a unique PK profile. The long-term safety and efficacy of RT-102 remains to be determined in future studies. If shown to be efficacious, RT-102 might substantially reduce the treatment gap that currently exists between injectable anabolic medication and oral antiresorptives. Beyond teriparatide, the RP, being agnostic to the specific payload, has the potential to transform many other injectable drugs to patient preferred oral pills.

AUTHOR CONTRIBUTIONS

A.K.D. was the study director and J.T.M. managed the study. M.I. is the inventor of the RP. J.T.M., A.K.D., M.H., J.V.D., J.P.B. and M.I. designed the study protocol. A.T.V., N.P., L.C.F. and A.Y. contributed to the development and aseptic manufacturing of drug products. M.I. and B.S. contributed to the development and manufacturing of RT-102. A.D. and A.B. conducted the evaluation of the enzyme-linked immunosorbent assay and analyses of the PK samples. J.T.M., A.K.D., M.H., A.D., L.C.F. and A.Y. contributed to data analysis and interpretation. The manuscript was written by J.T.M., A.K.D., A.Y., J.V.D., J.P.B. and M.H., and critically reviewed by all authors.

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The study was conducted at Nucleus Network in Australia with Dr. Ofer Gonen as the PI.

CONFLICT OF INTEREST STATEMENT

All authors, except John Bilezikian and Ofer Gonen, were employees of the company at the time the work was conducted. There are no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on request.

CONSENT FOR PUBLICATION

All authors read and approved the final manuscript for publication.

ETHICS APPROVAL

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.

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