Patient Preference and Adherence

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ORIGINAL RESEARCH

Preference for a Novel Oral Alternative to Parenterally Administered Medications

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Video abstract

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Background: Rani Therapeutics is developing a robotic pill (RP), an oral drug delivery platform called RaniPill™ that can deliver a number of biotherapeutics with high bioavailability; eliminating the need for injections. While patients in general prefer oral to injectable therapies, preference for a more frequent oral regimen compared to a less frequent injectable regimen is unknown. Two marketing surveys were conducted to gather data on preference for oral versus injectable therapies. A clinical study gathered data on participant preference for oral pills vs injections before and after swallowing a Mock-RP capsule.

Methods: A total of 1689 adults taking injections (mean duration 3–7 years) to treat endocrine or inflammatory conditions were anonymously surveyed online for their preference to administer/prescribe medications orally via the RP. In the clinical study, 150 participants currently taking injections for chronic conditions evaluated the swallowability of a Mock-RP and completed a questionnaire regarding their preferences.

Results: Majority of respondents surveyed stated they would be willing to convert to an oral alternative over their current parenteral therapy regardless of drug or disease. In the clinical study, all participants were able to swallow the Mock-RP and 91% indicated their preference for the oral route versus their current parenteral route of drug administration. Survey respondents and those in the clinical study using frequent injections were more willing to select a once-daily capsule compared to those injecting infrequently. Even study participants who inject infrequently (≥monthly: 80%) would prefer a once-daily pill over their injection regimen.

Conclusion: Patients taking injections and prescribing physicians strongly prefer oral dosing to parenteral administration of biologics even if dosing frequency with the oral option, such as the RP, is increased.

Keywords: oral drug delivery, biotherapeutic, robotic pill, once-daily pill, swallowability

Introduction

Patient compliance (ie, adherence to the treatment regimen as prescribed) significantly impacts the effectiveness of a therapy and is strongly influenced by patients' preference for a particular method of medication or drug delivery. Patient preference is influenced by a variety of factors, both personal and societal, thus challenging health care professionals in finding and maintaining appropriate treatment options particularly for chronic diseases. Patients often prefer oral over injectable medications not just due to inconvenience but also because of fear of needles, incorrect dose administration, pain of injection, and stigma around injectables.[1–4] A study of patients with type 2 diabetes (T2DM) found that 82% of participants preferred a once-daily oral treatment over a once-daily injectable, with 58% ranking the route of administration as the most important factor driving their preference.[5]

Independent of the mode of medication delivery (oral or injectable), patients also express preference for less frequent administration (eg, weekly over daily).[6–8] Patients with multiple sclerosis were also more compliant with drug administration every 6 months compared to more frequent injections or even oral dosing.[9] A once monthly injection for osteoporosis was preferred to once weekly as it was more convenient.[10] Asthma patients and their physicians expressed strong preference for less frequent injection of biologics to manage their disease[6] and a patient preference study

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comparing daily versus weekly injectable T2DM therapies found that injection frequency was the most important factor compared to type of device, needle size and pain, refrigeration, and injection-site reactions, with participants strongly preferring less frequent administration.[11] Patients prefer less frequent administration as they perceive them to be more convenient, to interfere less with work and social life, and to improve adherence.[1–4,12,13] However, even with less frequent injections, a significant number of patients skip injections or fail to adhere to their treatment regimen.[14] Thus, providing an oral alternative for many of these patients would improve compliance and health outcomes.

Although patients prefer orally administered medications, biotherapeutics, which must be administered via injection, represent an important and growing modality for the treatment of chronic inflammatory,[6] endocrine[15] and autoimmune diseases.[16] Further, the number of drugs that must be administered via injections continues to grow because biologics and biosimilars are highly effective treatments for illnesses such as asthma, diabetes, plaque psoriasis, rheumatoid arthritis, Crohn's disease, and osteoporosis. Unfortunately, long-term administration of injections is a serious burden for the patient and interferes with comfort, quality of life, and particularly adherence with therapy.[17–19] Thus, development of an oral delivery modality for biotherapeutics is a highly desirable goal for patients and caregivers, providing an alternative to injections would improve adherence and persistence, as well as clinical outcomes.

To date, only a couple of oral biologics have been approved. This is attributed to quick degradation and limited absorption of biologics in the GI tract. New oral biologic technologies will need to overcome the GI tract barriers (eg, harsh stomach conditions, small intestine secreted proteases and peptidases, inefficient absorption by intestinal epithelium, etc.) to address low bioavailability with current oral options.[20]

With few exceptions, patients with immune or endocrine diseases have had no oral drug options to injectable biotherapeutic medications. Thus, there does not appear to be any published research comparing patient preferences for oral medication delivery to biweekly, monthly, or less frequent injectable biologic administration. This research was prompted by the development of the RaniPill, an orally ingestible robotic pill (RP) which can deliver a variety of biotherapeutic drugs with bioavailability similar to subcutaneous injections.[21–23] The RP can potentially replace injections for many biotherapeutics. The purpose of the two marketing surveys was to understand the preference of current injection users and prescribing physicians for a once-daily oral pill similar to the RP rather than their frequent or infrequent injectable medication. In addition, we conducted a clinical study to evaluate the patient's experience with swallowing the RP and whether this experience influenced their preference for an oral alternative to their injectable medication.

Materials and Methods

Marketing Surveys

Two computer-assisted WEB marketing surveys were developed and conducted in the United States in September 2017 (Market Survey 1) and April to June 2021 (Market Survey 2) to obtain opinions and interest for a once-daily oral pill alternative to injectable medication. The surveys were developed and administered by Frost & Sullivan (Santa Clara, CA, San Antonio, TX). Both surveys were given to a targeted segment of people using injectable medications for diabetes, osteoporosis, or inflammatory conditions, and physicians currently treating patients with those conditions. Both injection users and clinicians were provided with information about the RP prior to the survey. To eliminate any bias regarding cost or effectiveness, respondents were told that the pill would be cost-neutral and as safe and effective as an injection. In addition, prescribing physicians were told that the pill would be an FDA approved product and deliver similar serum exposures as a subcutaneous injection, with comparable latency, pharmacokinetics, bioavailability and duration of action.

Respondents were chosen for the marketing surveys if they were currently on injections for diabetes and/or inflammatory conditions or physicians who specialize in endocrinology, gastroenterology, or rheumatology. Market Survey 1 required a minimum of 200 respondents per type of diabetes (I or II) and a minimum of 50 per inflammatory condition (rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, psoriasis). Type I and Type II diabetes respondents had been treated with basal insulin for an average of seven and four years, respectively, and the inflammatory condition group had been treated on average for 3–4 years. Market Survey 2 required a minimum of 100 respondents per injectable drug (Simponi, Entyvio, Stelara, Prolia, Evenity Cosentyx), and a minimum of 200 physicians.

The average number of years respondents had been using their specific drug was 3.3 years with the longest duration of drug use being Stelara® (4.3 years) and the shortest being Cosentyx® (2.3 years).

The marketing surveys collected information from respondents on the likelihood of choosing a pill alternative, current satisfaction with injections, expected satisfaction with the pill, and the relative importance of dosing frequency compared with other variables.

The survey respondents previously opted to participate in healthcare market research. The survey link was provided to the respondents directly; however, no respondent identifying information was collected.

Screener questions were utilized to verify that respondents were the target population for the survey. Current injection users were asked their age, current injectable drug, and other drugs they were using. Physicians were asked to indicate their field of practice and the disease state(s) they treated in their practice.

All qualified respondents received the same questionnaire specific to if they were using injections or a prescribing physician. Frost & Sullivan received the survey data directly and provided data summaries to Rani Therapeutics.

Clinical Study

In addition to the marketing surveys, we conducted a prospective, single-center, open-label, observational study (NCT04911296) in the United States in which a mock RP (Mock-RP) was offered as a potential oral alternative to patients who were currently taking biotherapeutics via injections for their chronic conditions (eg, diabetes [I or II], rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, psoriasis, growth hormone deficiency, hemophilia A). This clinical study was reviewed and approved by the Advarra Institutional Review Board (Columbia, Maryland), conducted in accordance with the principles stated in the Declaration of Helsinki, and all participants signed the informed consent prior to performing any study required procedures. Similar RP educational information from the marketing surveys were provided to the study participants.

The Mock-RP (manufactured by Rani Therapeutics) is a 000 size HPMC capsule, with the same shape, size, texture, and weight of the RP but did not contain the drug delivery mechanism. The Mock-RP was weighted with potato starch, enteric-coated with colorant and a lubricious coating to create a replica of the RP.

A total of 150 participants were included with 50 in each of the following age (years) groups: 21–50, 51–65, 66–75. Key inclusion criteria included participants aged 21–75 years currently taking an injection to treat a chronic disorder. Key exclusion criteria included history of dysphagia, dementia, and participant self-reports issues with swallowing pills. Each participant completed a paper questionnaire assessing their thoughts on an alternative therapy in an oral pill form before attempting to swallow the Mock-RP (Appendix 1). After swallowing the Mock-RP, participants completed another paper questionnaire assessing their ability to swallow the capsule (Appendix 1). Swallowability and texture/feel of the Mock-RP were assessed for the entire study population and stratified by age, prior pill swallowing history, prior injection use, and frequency of current injections.

Potential bias for the study was minimized by screening participants to confirm eligibility prior to swallowing the Mock-RP; site and sponsor personnel were trained on their respective aspects of the study using standardized training materials; study personnel were trained on and were required to follow the protocol; study investigators provided financial disclosure in compliance with 21 CFR 54 – Financial Disclosure by Clinical Investigators; and monitoring was conducted to ensure adherence to Good Clinical Practice and the study protocol and accurate data reporting.

Data Analysis

No formal hypothesis testing was performed in the surveys or clinical study. Survey and clinical study data are summarized by category using frequency tables and presented by participant counts and/or relative percentages. Variables are summarized and values reported as mean, minimum, and maximum. MS Excel was used for data analysis for surveys and clinical study. SAS (SAS Institute Inc.) was used when testing for statistical significance in clinical study. P-values (Fisher's exact test) of all tests were reported without any correction for the multiplicity of tests performed.

Results

Market Survey 1 Sample

Diabetics (Type I: n = 208; 36%; Type II: n = 369; 64%) for this survey were 52% female with a mean age of 41 years (Table 1). Prescribing endocrinologists (N=61) indicated that 66% Type I and 56% Type II of their diabetic patients were prescribed basal insulin injections. GLP-1 drugs were prescribed for 53% and mealtime insulin injections for 56% of all their diabetic patients. Diabetics (81% of Type I and 86% of Type II) indicated their disease was either extremely well or somewhat well managed by their insulin injections. Endocrinologists indicated only 68% of their patients (both Type I and Type II) had their diabetes extremely well or somewhat well managed by their injections and that 34% of their patients fail to inject insulin at the same time every day.

Respondents with an inflammatory condition treated with Humira were 58% female with a mean age of 43 years and reported taking Humira every 10 to 12 days, with 62% skipping injections frequently (Table 2). Contrary to the diabetic population, gastroenterologists and rheumatologists indicated their patients' inflammatory conditions were well controlled and only 14% forget to take the injection.

Market Survey 1 Results

When diabetics were asked for their preference if a basal insulin was available as an oral pill, 87% indicated they would switch from their current injection regimens to a once-daily pill alternative. Endocrinologists were asked a similar question regarding potential changes to their prescribing pattern for their diabetic patients and 89% said they would switch to prescribing a once-daily pill. A small number of injection users (5%) and physicians (3%) were not likely to

Table 1 Demographics and Medical/Medication History for the Respondents with Diabetes in Survey

Number of Respondents with Diabetes (N)	**577**
Gender n (%)	
Female	300 (52%)
Male	277 (48%)
Age, years	
Mean (min-max)	41 (18–85)
Respondents with Conditions n (%)[a]	
Diabetes (Type I)	208 (36%)
Diabetes (Type II)	369 (64%)
Respondents Taking Injections n (%)[a]	
Basal Insulin[b]	577 (100%)
GLP-1 Agonist[c]	427 (74%)
Fast Acting Insulin[d]	387 (67%)
Treatment Duration n (%)	
< 1 year	30 (5%)
1–5 years	361 (63%)
> 5 years	186 (32%)

Notes: [a]Not mutually exclusive; [b]Lantus®, Tresiba®, Levemir®, Toujeo®, Basaglar®; [c]Trulicity®, Ozempic®, Victoza®, Bydureon®; [d]Novolog®, Humalog®, Apidra®.
Abbreviations: min, minimum; max, maximum.

Table 2 Demographics and Medical/Medication History for the Respondents with Inflammatory Conditions in Market Survey 1

Number of Respondents with Inflammatory Conditions (N)	**501**
Gender n (%)	
Female	291 (58%)
Male	210 (42%)
Age, years	
Mean (min-max)	43 (18–77)
Respondents with Conditions n (%)[a]	
Rheumatoid Arthritis	291 (58%)
Psoriasis	256 (51%)
Crohn's Disease	105 (21%)
Ulcerative Colitis	80 (16%)
Respondents Taking Medications n(%)[a]	
Humira® (adalimumab)	501 (100%)
Treatment Duration n (%)	
< 1 year	45 (9%)
1–5 years	389 (786%)
> 5 years	67 (13%)

Notes: [a]Not mutually exclusive.
Abbreviations: min, minimum; max, maximum.

adopt a once-daily pill alternative. Additionally, respondents (injection user; physician) reported a pill alternative may be mostly better in terms of pain (55%; 77%), ease of use (53%; 77%), managing and disposing of products (52%; 80%), ease of transportation/use away from home (51%; 74%), and dealing with stigmas (50%; 79%), but remembering to take the pill might remain challenging for patients (44%; 56%). Overall, physicians in general were more positive about the pill advantages than current injection users.

Respondents with inflammatory disease who use injectable drugs but inject less frequently than diabetics provided similar responses regarding the advantages of replacing their injections with a pill (Table 3). Eighty-eight percent of current injection users with inflammatory disease (independent of the disease type), and 86% of their rheumatologists and gastroenterologists would switch to using/prescribing a pill if it were available. Most of the surveyed physicians (70–94%) indicated a once-daily pill alternative would improve patient compliance rate for both diabetics and patients with inflammatory conditions. Endocrinologists (81%) indicated that if an insulin pill was available, they would likely start their diabetic patients on insulin sooner.

Market Survey 2 Sample

Current injection users surveyed were 72% male with an average age of 37.7 years and taking one of six different drugs (Simponi®, Entyvio®, Stelara®, Prolia®, Evenity®, and Cosentyx®) for various inflammatory conditions (Table 4). Endocrinologists (N=84) and rheumatologists (N=117) who prescribe injection medications were surveyed about the

Table 3 Patients with Inflammatory Conditions and Physicians (Gastroenterologists and Rheumatologists) Perception of an Alternative Oral Therapy Compared to Current Injection Therapies

	Patients w/ Inflammatory Conditions (N=501) n (%)			Gastroenterologists and Rheumatologists (N=118) n (%)		
	Better	Same	Worse	Better	Same	Worse
Pain	296 (59%)	105 (21%)	100 (20%)	89 (75%)	11 (9%)	18 (15%)
Ease of use	271 (54%)	115 (23%)	110 (22%)	90 (76%)	17 (14%)	12 (10%)
Easier to dispose of product	286 (57%)	105 (21%)	110 (22%)	87 (74%)	22 (19%)	9 (8%)
Easier for travel from home	271 (54%)	140 (28%)	90 (18%)	64 (54%)	31 (26%)	22 (19%)
Dealing with stigma of injections	220 (44%)	155 (31%)	125 (25%)	90 (76%)	17 (14%)	12 (10%)
Easier to manage with other medications	245 (49%)	140 (28%)	115 (23%)	61 (52%)	30 (25%)	27 (23%)
Easier to remember	271 (54%)	125 (25%)	105 (21%)	51 (43%)	40 (34%)	27 (23%)

Table 4 Demographics and Medical/Medication History of Respondents in Market Survey 2

Number of Respondents (N)	611
Gender n (%)	
Female	169 (28%)
Male	442 (72%)
Age, years	
Mean (min-max)	39 (18–78)
Respondents with Conditions[a] n (%)	
Rheumatoid Arthritis	223 (36%)
Psoriasis	164 (27%)
Crohn's Disease	184 (30%)
Ulcerative Colitis	162 (27%)
Psoriatic Arthritis	238 (39%)
Osteoporosis	161 (26%)
Ankylosing Spondylitis	111 (18%)
Non-Radiographic Axial Spondyloarthritis	74 (12%)
Other conditions	19 (3%)[b]
Respondents Taking Medications[a] n (%)	
Simponi® (golimumab)	102 (16.7%)
Entyvio® (vedolizumab	103 (16.9%)
Stelara® (ustekinumab)	100 (16.4%)
Evenity® (romosozumab)	101 (16.5%)

(*Continued*)

Table 4 (Continued).

Number of Respondents (N)	611
Prolia® (denosumab)	103 (16.9%)
Cosentyx® (secukinumab)	102 (16.7%)
Treatment Duration n (%)	
< 1 year	28 (4.6%)
1–5 years	459 (75.1%)
> 5 years	124 (20.3%)

Notes: [a]Not mutually exclusive; [b]N = 1: allergies, anemia, bipolar disorder, bursitis, chronic B12 nutritional deficiency, hidradenitis suppurativa, low iron, multiple sclerosis, prediabetes, schizoaffective disorder, weight management for obesity.
Abbreviations: min, minimum; max, maximum.

type of injection medications used by current injection users in this survey, as well as additional injection medications for non-inflammatory diseases such as osteoporosis, hypoparathyroidism, and pediatric/adult growth hormone deficiency.

Regardless of the disease or drug used, 77% (69–81%) of the current injection users reported an injection frequency of either weekly or monthly.

Physicians reported similar results for most of their patients (across all diseases) using injectable drugs for an average of 3.3 years with adult human growth hormone deficient patients being the longest (5.1 years).

Market Survey 2 Results

While most respondents (73%) reported it is easy to remember their dosing schedule, about 2 of every 3 current injection users surveyed across all drugs (57–71%) reported taking their injections on schedule. Most were also satisfied with disposing of the drug and injection products (70%) and injection site pain (71%). However, rheumatologists and endocrinologists (39% and 60%) thought their patients were less satisfied with using injectable drugs than what was reported by the current injection users.

Current injection user preference was high for a daily oral alternative to their injectable medication regardless of the drug they were taking (Table 5). Two out of three (64–77%) surveyed said they either "Would Definitely Switch" or

Table 5 Percent of Patients Likely to Convert to a Pill Regimen Categorized by Their Current Injectable Drug in Market Survey 2

Potential Pill Dosing Regimens	Current Injectable Drug n (%)					
	Simponi (N=102)	Evenity (N=103)	Cosentyx (N=102)	Entyvio (N=103)	Stelara (N=100)	Prolia (N=103)
Daily Pill	75 (74%)	75 (73%)	77 (75%)	79 (77%)	64 (64%)	78 (76%)
One week series of pills taken **every month**	73 (72%)	78 (76%)	84 (82%)	80 (78%)	65 (65%)	80 (78%)
One week series of pills **every two months**	80 (78%)	79 (77%)	82 (80%)	79 (77%)	71 (71%)	80 (78%)
One week series of pills **every three months**	78 (76%)	80 (78%)	89 (87%)	81 (79%)	63 (63%)	85 (83%)
One week series of pills taken **every six months**	69 (68%)	81 (79%)	85 (83%)	82 (80%)	72 (72%)	82 (80%)

"Would Switch" to an oral alternative. There was little difference (3–12% variability depending on drug) in enthusiasm between the five proposed dosing schedules suggesting the enthusiasm was for the oral option and not necessarily the schedule. However, there was an exception: some reported taking medications at frequencies different from the prescribed schedules and some reported using more than one drug; segregating data based on user-reported higher injection frequency indicated that users who inject more frequently had higher enthusiasm about an oral alternative than those who injected less frequently (Table 6). In general, most current injection users who inject every 3–6 months still preferred an oral medication, and 55% who self-reported an injection frequency of once every six months would still prefer to switch to a once daily oral alternative.

Physicians were asked what percentage of their patients (All patients: 100%, Most patients: 75%, Half of patients: 50%, Some patients: 25%, No patients) currently injecting medications they believe would prefer to switch to an oral medication. Across all drugs administered, except for Prolia®, 84% of physicians indicated that more than 50% of their patients would prefer an oral alternative to their current injection and 65% of physicians believed that more than 75% of their patients would prefer to switch. Only 2–8% of physicians reported they have patients who will never switch. Physicians believed that frequency of injection may determine the likelihood of patients switching to an oral medication as less than 50% of physicians reported that a majority (75%) of their patients injecting Prolia® every 6 months would switch to an oral medication. In contrast, 84% of endocrinologists prescribing hormonal drugs requiring a daily injection believe that most (75–100%) of their patients would switch to an oral replacement.

When asked about the impact of a once-daily pill on patient compliance, 74% of the physicians felt compliance would improve in patients using daily injectables, compared with 52% of physicians who think compliance would improve for patients injecting drugs less frequently (1–3-month intervals). With all possible drug treatments, 72% of endocrinologists and 67% of rheumatologists would use an oral alternative as their first line of therapy independent of the patient's age, disease severity or how long the patient used injectable medications. Endocrinologists suggested that introducing a once-daily pill will result in earlier initiation of basal insulin in diabetics: by <1 year (23%), by 1–2 years (25%) and by 3+ years (33%) than current treatment practices.

Clinical Study Sample

A total of 152 participants were enrolled with 150 of them attempting to swallow the Mock-RP. Two participants were excluded during screening: one participant on an insulin pump with no injections and another who was using ocular injections. Participants were 57% female (Table 7), taking at least one injection therapy for their chronic condition, and most (97%) were also taking oral medicines in pill form (Table 8).

Table 6 Percent of Patients Likely to Switch to an Oral Pill Based on Self-Reported Injection Frequency in Market Survey 2

Potential Pill Dosing Regimens	Current Injection Frequency n (%)[a]				
	Weekly (N=217)	Monthly (N=256)	Every 2 Months (N=72)	Every 3 Months (N=28)	Every 6 Months (N=31)
Daily Pill	171 (79%)	192 (75%)	156 (61%)	14 (50%)	17 (55%)
One week series of pills **every month**	174 (80%)	202 (79%)	156 (61%)	17 (61%)	17 (55%)
One week series of pills **every two months**	178 (82%)	202 (79%)	177 (69%)	15 (54%)	20 (65%)
One week series of pills **every three months**	178 (82%)	205 (80%)	182 (71%)	17 (61%)	20 (65%)
One week series of pills **every six months**	178 (82%)	200 (78%)	174 (68%)	16 (57%)	21 (68%)

Note: [a]Seven respondents indicated a frequency different from these defined categories.

Table 7 Demographics and Medical/Medication History of Participants in the Clinical Study

Number of Participants (N)	**150**
Gender n (%)	
Female	85 (57%)
Male	65 (43%)
Age, years	
Mean (min-max)	58 (21–75)
Conditions[a] n (%)	
Diabetes (Type I)	107 (67.3%)
Diabetes (Type II)	21 (13.2%)
Rheumatoid Arthritis	6 (3.8%)
Migraines	5 (3.1%)
Low Testosterone	2 (1.3%)
Psoriasis	2 (1.3%)
Osteoporosis	2 (1.3%)
Ulcerative Colitis	1 (0.6%)
Psoriatic Arthritis	1 (0.6%)
Ankylosing Spondylitis	1 (0.6%)
Other conditions	11 (6.9%)[b]
Medications[a] n (%)	
Prolia® (denosumab)	1 (0.6%)
Cosentyx® (secukinumab)	1 (0.6%)
Humira® (adalimumab)	1 (0.6%)
Basal Insulin	83 (55.3%)
GLP-1 Agonist	58 (38.7%)
Fast Acting Insulin	52 (34.7%)
Other Medications[b]	38 (25.3%)
Treatment Duration n (%)	
< 1 year	16 (10.7%)
1–5 years	29 (39.3%)
> 5 years	75 (50%)

Notes: [a]Not mutually exclusive; [b]21 medications reported at a < 3% rate.
Abbreviations: min, minimum; max, maximum.

Clinical Study Results

Duration of use of injectable medications was significantly different between age groups (p = 0.026) with the 21–50 age group having the highest number of participants who started injections within the last year (20%) while the 51–65 age group used injectable drugs for more than 5 years (64%). There were no significant differences between the age groups

Table 8 Injection and Pill History of the Study Participants

	21–50 Years (N=50)	51–65 Years (N=50)	66–75 years (N=50)	Total (N=150)
Years using injections n (%)				
<1 Year	10 (20%)	2 (4%)	4 (8%)	16 (11%)
1–5 Years	18 (36%)	16 (32%)	25 (50%)	59 (39%)
>5 Years	22 (44%)	32 (64%)	21 (42%)	75 (50%)
Currently taking pills n (%)				
No	1 (2%)	2 (4%)	1 (2%)	4 (3%)
Yes, 1–3 Daily	21 (42%)	14 (28%)	14 (28%)	49 (33%)
Yes, >4 Daily	28 (56%)	34 (68%)	35 (70%)	97 (65%)

regarding the number of pills participants were currently taking and whether the participants would select a pill instead of injection therapy, with 94% of all participants indicating they would select a pill.

Participants were asked to swallow the Mock-RP and complete a post-swallow questionnaire. All 150 participants successfully swallowed the Mock-RP. When asked to describe the experience of swallowing the pill, 76% (114/150) said it was easy to swallow and 17% (25/150) said it was large but easy to swallow. There was no difference in responses across age groups. When asked to rate the ease of swallowing the pill from easy to difficult, no one rated it "Difficult" to swallow (Table 9). Participants felt the pill had no taste (93%), it was smooth (75%), and not sticky (83%). Importantly, 91% (136/150) said they would prefer this pill to their current injection with only 9% (14/150) of participants preferring the injection. Reasons for why a participant would not take the pill included: too large (6); because they thought the pill might be too pricey for insurance to cover (1); they tend to forget to take pills (2); they currently take too many pills (3); the pill needs more research before they would take it (1); they preferred their injection (1).

Table 9 Participants Responses to Questions Related to Pill Characteristics After Swallowing the Mock-RP

Groups	21–50 Years (N=50)	51–65 Years (N=50)	66–75 Years (N=50)	Total (N=150)
Able to swallow the pill n (%)				
Yes	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Describe swallowability n (%)				
Easy	36 (72%)	37 (74%)	41 (82%)	114 (76%)
Large Pill – Easy	10 (20%)	9 (18%)	6 (12%)	25 (17%)
Challenging due to size	4 (8%)	3 (6%)	1 (2%)	8 (5%)
No Comment	0 (0%)	1 (2%)	2 (4%)	3 (2%)
Take pill instead of injection n (%)				
Yes	44 (88%)	48 (96%)	44 (88%)	136 (91%)
No	6 (12%)	2 (4%)	6 (12%)	14 (9%)

(*Continued*)

Table 9 (Continued).

Groups	21–50 Years (N=50)	51–65 Years (N=50)	66–75 Years (N=50)	Total (N=150)
Rate ease of swallowing n (%)				
Easy	31 (62%)	31 (62%)	27 (54%)	89 (59%)
Somewhat easy	8 (16%)	14 (24%)	15 (30%)	37 (25%)
Neutral	5 (10%)	4 (8%)	6 (12%)	15 (10%)
Somewhat difficult	6 (12%)	1 (2%)	2 (4%)	9 (6%)
Difficult	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pill Taste n (%)				
No Taste	45 (90%)	48 (96%)	45 (90%)	138 (93%)
Feel of pill on tongue n (%)				
Smooth	36 (72%)	42 (84%)	35 (70%)	113 (75%)
Somewhat Smooth	11 (22%)	6 (12%)	12 (24%)	29 (19.3%)
Stickiness on roof of mouth n (%)				
Does not Stick	40 (80%)	43 (86%)	41 (82%)	124 (83%)
Sticks a Little	8 (16%)	3 (6%)	7 (14%)	18 (12%)

Table 10 Participants Preference for Oral Pill Before and After Swallowing the Mock-RP, According to Their Current Injection Frequency

Participant Current Injection Frequency	Preference for Oral Pill			
	Daily n/N (%)	Every 2 weeks n/N (%)	Weekly n/N (%)	≥Monthly n/N (%)
Before swallowing	95/101 (94%)	2/2 (100%)	34/36 (94%)	9/10 (90%)
After swallowing	92/102 (90%)	2/2 (100%)	34/36 (94%)	8/10 (80%)

There was a small, but not statistically significant decrease (94% pre- vs 91% post-, $p>0.05$) post-swallow in the preference for the Mock-RP after swallowing the pill compared to pre-swallow. There were no statistically significant differences in responses when stratified by age groups ($p>0.05$). Responses to the pre- and post-swallow questionnaire were stratified to evaluate if injection frequency (daily, weekly, every 2 weeks, and ≥monthly) influenced a participant's response on choosing a pill (Table 10). When comparing injection frequencies, participants taking injections monthly or longer intervals reported a lower preference for selecting a daily pill instead of their current injection, as expected.

There were no statistically significant differences in responses for any of the questions in the post-swallow questionnaire when stratified by pill swallowing history (No history, 1–3 pills daily, 4 or more pills daily). Similarly, there were no statistically significant differences in responses for any of the questions in the post-swallow questionnaire when stratified by duration of prior injection use (<1 year, 1–5 years, >5 years).

Discussion

Patient compliance (ie, adherence to the treatment regimen as prescribed) significantly impacts the effectiveness of a therapy and is strongly influenced by patients' preference for a particular method of medication or drug delivery; patient preference, in turn, is influenced by a variety of factors, personal (eg, fear of swallowing pills/taking injections, associated pain/embarrassment, frequency of dosing), societal (eg, cost/access/drug availability), and medical (disease state/patient age/cognition). The present series of market surveys are the first that we are aware of to provide clear and unambiguous preference data that people currently taking injections would overwhelmingly prefer to switch to an oral alternative, even if it required far more frequent (eg, daily) dosing compared to their present injection schedules. Our preference data are consistent with previous studies which reported that the pain and inconvenience of chronic injections can lead to reduced adherence, poor quality of life and compromised disease management.[17,24–26]

These market surveys were prompted by our progress in developing a versatile, orally ingestible drug delivery platform in the form of a RP that can pass through the stomach intact and deliver its payload transenterically.[21] The RP has been shown to effectively deliver a number of biotherapeutics in animal models[22,23,27–29] as well as in humans[21,30] with oral bioavailability comparable to SC injections.[30] The surveys were designed to evaluate the preference of current injection users, as well as prescribing physicians, for replacing their current injectable regimen with a more frequent (daily) oral pill like the RP, especially given the availability of newer, long-acting drugs with infrequent dosing regimens.

Survey data suggest that a significant number of respondents using injectable biotherapeutics, as well as the physicians who prescribe these drugs, would prefer an oral alternative. Not unexpectedly, people who inject more frequently overwhelmingly preferred a once daily pill in place of their injection. In fact, a pill a day alternative was preferred by 87% of diabetics taking basal insulin daily, and 88% injecting Humira every two weeks. Our findings are consistent with published data demonstrating that diabetic patients presented with options for a once weekly injection, or a once daily oral medication preferred the oral route.[15,31,32] This is consistent with published data that severe asthmatics currently on biologic therapies reported mode of administration as one of the top 3 most important factors when assessing medication features.[6]

However, it was surprising that even among people who self-reported injecting medications only twice a year, 55% would prefer a once daily oral pill and 68% would substitute their injections for a one-week series of pills every six months. These data appear to be the first to report that people on an infrequent injection schedule would still prefer an oral alternative even if it required more frequent dosing.

Patient preference for less frequent injections or for an alternative to their painful injectable medications has encouraged development of less painful injectors,[33–36] or more long-acting medications which require less frequent injections. Development of therapeutic monoclonal antibodies with long half-life has revolutionized treatment of many chronic diseases and, in several cases, improved patient persistence and adherence.[37–39] In Market Survey 2, current injection users reported good adherence and persistence such that 2/3rd said they injected their medication on schedule, and most had continued their therapy for more than 3 years. However, despite their satisfaction, their current infrequent injectable regimen, more than 2/3rd (64–77%) would switch to an oral, once-daily medication (regardless of dosing frequency) if it were available. The reasons behind their preference for a more frequent oral pill regimen over a less-frequent injection regimen varied but were similar to issues expressed by people who inject frequently (pain, inconvenience, stigma), suggesting that reducing injection frequency alone does not address all concerns regarding injections.

In Market Survey 2, people who inject frequently (weekly or monthly) indicated no significant preference for pill dosing frequency when asked their preference for a once-daily pill or a one-week series of pills every month, every two/three months, or every six months. A majority (75–82%) who inject weekly/monthly would prefer any of the regimens for an oral pill to their current injection regimen, whereas people who inject less frequently (every 2–6 months) showed a preference for less frequent pill dosing regimens, particularly people receiving Prolia every 6 months. Physician responses concur with current injection user data, as physicians who prescribe daily injectable medication believe most of their patients would readily switch to a once daily pill.

Although a majority of respondents using injectable medications indicated they prefer a pill, it was unclear whether they would continue to prefer a pill after swallowing the RP. Pill properties such as size, texture, smell, or taste determine whether a patient will consistently use oral medication as prescribed. It is estimated that 81% of adults in the United

States take pills every day and 54% report encountering pills that are hard to swallow with pill size and surface texture as the primary reasons.[40] The Mock-RP, like the RP, has a lubricious coating which renders the capsule sufficiently smooth to improve swallowability compared to other capsules in its size. Data from the swallow study show that all participants swallowed the Mock-RP in this study and 76% thought it was easy to swallow. Only 6% thought it was somewhat difficult to swallow, which is well below the general consensus.[40] Also, while older adults are more likely to have trouble swallowing large pills,[41,42] we observed no differences in ease of swallowing the Mock-RP between participants who were 66–75 years old and those who were 21–50 years old. Texture and taste also did not impact swallowability in any age group. Importantly, after their experience swallowing the Mock-RP, 91% of the participants stated that they would prefer this pill over their injection, including 80% of those who take injections infrequently.

Cultural, socioeconomic and ethnic backgrounds, as well as medical conditions contribute to patient preferences regarding medication and health care in general.[43,44] Providing patients with options for drug delivery such as the RP can only improve patient adherence and persistence to treatment. Globally, approximately 50% of type 2 diabetic patients experience suboptimal compliance with their injectable therapy, leading to poor glycemic control and associated increases in hospitalizations, mortality, and health care costs.[45–49] Reasons for poor patient compliance are multifactorial[50–53] but injection pain and injection frequency correlate with reduced persistence and adherence.[3] Persistence rates measured for one year were significantly higher for diabetic patients injecting weekly compared to those injecting daily.[54] In a separate study, patients expressed their preference for a once weekly injection over a daily injection.[11] However, adherence and persistence even with weekly injections was not ideal. A multi-year study of persistence and adherence of Israeli patients injecting Humira every 2 weeks reported 80% adherence across all inflammatory diseases but only 52.4% persisted taking the drug by year 3 with some patients discontinuing therapy within two years.[14] Data from our Market Survey 2 indicate that 66% of people injecting Humira every 10–12 days reported they frequently skip an injection. Thus, a significant number of current injection users are not adequately medicated and could benefit from an oral medication option.

In this regard, adherence and persistence for patients with multiple sclerosis were greater for oral medications compared to injectables,[55] and a multi-year review of published studies (2017–2022) examining adherence and persistence rates of all major antidiabetic medications found that rates were highest for oral medications and lowest for injectable medications.[56] However, oral medication may not meet the needs of all patients at all times and there may be situations where an injection may be preferable to oral medication. Data from our market surveys and clinical study show that some current injection users would likely not switch from infrequent injections to a more frequent oral pill. For example, less frequent, long-acting injectable medications for psychiatric patients were preferred over daily oral medications by physicians and family members because it was "easier to remember" for these specific patients.[57] Bisexual and gay men using HIV pre-exposure prophylactic medications preferred infrequent long acting injectables (43%) compared to daily oral medication (14%).[58] Adherence and persistence of pediatric patients prescribed oral medication is challenging[59] and patients with dysphagia[60,61] or pill aversion[42] certainly benefit from non-oral modes of drug delivery.

Providing patients, and their physicians, with additional medication delivery options for biologics, such as the RP, would be expected to improve adherence and persistence in many patients leading to better disease management and reduced hospitalizations. In Market Survey 1, endocrinologists (70%) thought that an oral medication would increase diabetic patient compliance and 91% indicated they would start patients on medications sooner if an oral option were available. Patients who inject medication frequently could benefit greatly from the availability of an oral alternative to their injectable medication and even patients who inject less frequently but prefer an oral medication would likely experience an improvement in persistence and adherence.

Conclusions

People currently taking injectable drugs to treat their chronic endocrine or inflammatory disease overwhelmingly preferred an oral route for medication than their current injection regimen. People injecting medications frequently (daily or weekly) were more likely to select a once-daily pill alternative compared to people who inject infrequently (every 6 months), although 55% of the latter still would prefer an oral alternative. Additionally, physicians also believed that compliance would be

improved with an oral alternative, including for patients taking infrequent injection therapy, indicating that they would begin treatment sooner if an oral drug was available. Participants in the swallowability study of a 000-sized replica of an enteric coated, orally ingestible robotic pill (Mock-RP) found it easy to swallow and, importantly, their preference for the oral route of drug delivery remained unchanged after swallowing the pill. Taken together, these data suggest that oral alternatives for injectable biotherapeutic medications are overwhelmingly preferred by both patients and physicians and are projected to significantly improve patient compliance, resulting in better disease management.

Data Sharing Statement

All data generated and analyzed from the clinical study are included in this published article. The pre- and post-swallow questionnaires are available in Appendix 1.

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Disclosure

All authors are paid employees of Rani Therapeutics, LLC or its affiliate and hold company stocks. The authors report no other conflicts of interest in this work.

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