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CP-0003

In Production

Pill Swallow Study Protocol

Revision »C - ECO-002760 Effective as of 2021/05/24 01:52:07 PM, Unshared

Category	Rani Therapeutics
Item Number	CP-0003
Revision	C
Item Name	Pill Swallow Study Protocol
Lifecycle Phase	In Production
Assembly Type	Not an assembly
Primary File	CP-0003 Rev C Pill Swallow Study Protocol 20210506
Associated Files	13 (plus 0 Supplier Item files)
Description	
Owner	Joshua Myers
Prototype Cost	
Production Cost	
Procurement Type	Off-the-Shelf (OTS)
Unit Of Measure	each
Item Creator	Joshua Myers
Item Created On	2021/02/02 01:50:18 PM

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ECO-002742

Pill Swallow Study Document Updates

Completed

Basic Information

Category	Engineering Change Order
Change Number	ECO-002742
Title	Pill Swallow Study Document Updates
Description	- CP-0003: Protocol updated to version B to change the pill contents from microcrystalline cellulose to potato starch and include a new exclusion criteria for allergies to mock-RaniPill components. - Summary of changes for the protocol added - Updated all CRFs to replace "subject" with "participant" and add a version date. Additional CRF Edits: - Screening CRF: Added new exclusion criteria for allergies to mock-RaniPill components. Moved Pill Swallow Assessment up the form. - Post-Swallow Questionnaire: changed VAS score from 0-10 to 0-4. - SAE Form: added "Final Outcome" field.
Associated Files	10 Reference File(s) + 0 Implementation File(s)
Routings	None specified
Approval Deadline	None specified
Effectivity	2021/04/28
Expiration Date	N/A (This is a permanent Change.)
Lifecycle Status...	Completed
...As Of	2021/04/28 03:38:17 PM
Creator	Joshua Myers
Created On	2021/04/23 06:53:40 AM
Submitter	Joshua Myers
Submitted On	2021/04/23 11:30:50 AM

Reason and Justification

Company/Project	Rani
Reason and Justification for Change	Protocol updated to version B to change the pill contents from microcrystalline cellulose to potato starch and add a new exclusion criteria. CRFs updated while creating the database and accommodating protocol changes.

Impact Assessment

Are other documents affected by this change?	No
Other affected documents	N/A
Design V&V Testing required?	No - Provide justification below.
Design V&V Testing additional info/justification	N/A
Process Validation required?	No - Provide justification below.
Process Validation additional info/justification	N/A
Risk Analysis update required?	No - Provide justification below.
Risk Analysis additional info/justification	N/A
Regulatory Action required?	No - Provide justification below.
Regulatory Action additional info/justification	N/A
Supplier/Partner notification required?	No
Supplier/Partner notification additional info	N/A
Training or re-training required?	No

Pill Swallow Study

Clinical Study Protocol

Sponsor:
Rani Therapeutics
2051 Ringwood Ave
San Jose, CA 95131

This study will be conducted in compliance with the Clinical Study Protocol, Good Clinical Practices and applicable local and national regulatory requirements.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRF	Case Report Form
CTA	Clinical Trial Agreement
CTM	Clinical Trial Material
CV	Curriculum Vitae
eCRFs	Electronic Case Report Forms
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GET	Gastric Emptying Time
GI	Gastrointestinal Tract
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICMJE	International Committee of Medical Journal Editors
IDT	Intestinal Deployment Time
IRB	Institutional Review Board
NSR	Non-Significant Risk
PI	Principal Investigator
SAE	Serious Adverse Event
US	United States

PROTOCOL SYNOPSIS

Title	Pill Swallow Study
Purpose	A Prospective Study Assessing Participant Experience with Swallowing a Mock Version of the RaniPill™ Capsule ("Mock-RP")
Phase of Clinical Trial	Non-significant risk
Test Device	Mock-RP: Standard 000 capsule shell filled with potato starch weighing similar as the RaniPill™ Capsule, enteric-coated with colorant and lubricous coating
Indication for Use	N/A
Study Objective	Assess a participant's ability to swallow a Mock-RP.
Sample Size	Up to 200 participants will be enrolled with up to 150 participants attempting to swallow the Mock-RP: 30 to 50 participants in each age group. Participation inclusion in an age group stops at 50 participants.
Follow-up	Assessment of the Mock-RP will occur the same day as swallowing the pill. No additional follow-up is anticipated.
General Study Design	A prospective, single-center, open-label, single-arm, observational study enrolling up to 200 men and women volunteers age ≥21 currently using injection therapy to treat chronic disorders (e.g., diabetes (I or II), rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylolisthesis, psoriasis, growth hormone deficiency, hemophilia A) recruited from the general population with up to 150 participants attempting to swallow the Mock-RP after passing protocol required screening. A total of 30 to 50 participants will be included in each of the following age ranges: 21-50, 51-65, 66-75. Participants must meet all inclusion and none of the exclusion criteria prior to attempting to swallow the Mock-RP. Participants will complete a questionnaire on their thoughts on an alternative therapy in pill form. Upon completion of the questionnaire, participants will be requested to swallow a Mock-RP. The Mock-RP will be a standard 000 capsule filled with potato starch weighing similar to the RaniPill™ Capsule. The capsule is protected by an enteric coating with colorant and lubricious coating allowing intact passage through the stomach into the jejunum, where the pH starts dissolving the coating; completely dissolving in the small intestine. After swallowing the Mock-RP, the participant will complete the questionnaire assessing swallowability of the Mock-RP. If the participant was unable to swallow the Mock-RP, they will be asked to attempt to swallow a Calcium dietary supplement (Rapid Release Calcium in Liquid Softgel). Anticipated participant duration is approximately 1 hour.
Inclusion Criteria	Individuals eligible to participate in this study must meet all the following criteria: 1. Participant age is 21 – 75 years 2. Participant understands the nature of the study, is willing to comply with protocol defined evaluations, and provide written informed consent 3. Participant currently taking injections to treat a chronic disorder 4. Non-pregnant, non-lactating female NOTE: Females who are of childbearing potential must have had a negative pregnancy test on day of screening

Exclusion Criteria	Individuals eligible to participate in this study must not meet any of the following criteria: 1. Active case of COVID-19. 2. History of Dysphagia. 3. History of dementia (e.g., Alzheimer's, vascular dementia, dementia with Lewy bodies, etc.). 4. Participant self-reports issues with swallowing pills. 5. History of drug or alcohol abuse or any other factor that, in the Investigator's opinion, may interfere with the participant's ability to cooperate and comply with the study procedures. 6. History of allergic reaction to a component of the Mock-RP 7. History which, in the investigator's judgement, makes the participant ineligible or exposes the participant to unacceptable risks
Study Endpoints	- Percent of participants successfully swallowing the Mock-RP as reported on the questionnaire. - Assess if participant would choose a pill instead of their current injection therapy if a pill becomes available. - Participant experience with swallowing Mock-RP stratified by number of years using injections. - Participant experience with swallowing Mock-RP stratified by age (21-50, 51-65, 66-75 years). - Participant experience with swallowing Mock-RP stratified by frequency of injection treatment. - All adverse events categorized by type and frequency.
Clinical Trial Material (CTM)	Mock-RP
Sponsor:	Rani Therapeutics 2051 Ringwood Ave San Jose, CA 95131

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1 INTRODUCTION

1.1 Study Purpose

Rani Therapeutics is sponsoring the Pill Swallow Study, a prospective, single-center, open-label, single-arm, observational study assessing participant experience with swallowing the Mock-RP.

1.2 Study Scope

This study will be conducted at one site in the U.S. Up to 200 participants will be enrolled (consented) and up to 150 will attempt to swallow the Mock-RP after passing protocol required screening. Study duration is expected to be approximately three months.

1.3 Governing Regulations

The Mock-RP is investigational and classified as a non-significant risk device in the U.S. This Clinical Investigation Plan (CIP) will not be submitted to the FDA for approval. The study will be conducted per 21 CFR Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), and 56 (Institutional Review Boards) and conducted in accordance with the relevant parts of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki and the individual country laws and regulations, whichever afford greater protection to participants. Participating sites will obtain IRB approval prior to beginning study.

2 BACKGROUND AND JUSTIFICATION

The RaniPill™ Capsule is an ingestible robotic pill, based on 000 (31 mm by 11 mm) size capsule designed to deliver biopharmaceuticals into the small intestinal wall. The goal of the RaniPill™ Capsule is orally deliver biologics which are currently given via subcutaneous, intramuscular or intravenous injections. The current study will evaluate the ease of swallowing of a pill similar in size to RaniPill™ Capsule.

2.1 Mechanism of Action

The RaniPill™ Capsule needs to be swallowed whole to keep its internal delivery mechanism intact. The RaniPill™ Capsule remains intact in the stomach, protected by the enteric coating. As it leaves the stomach and advances along the small intestine by peristalsis, the enteric coating starts to dissolve with the rise in pH. Dissolution of the enteric coating and capsule shell exposes the reaction valve to the intestinal fluid, causing its dissolution and enabling the mixing of citric acid and potassium bicarbonate. The production of carbon dioxide inflates and stabilizes the balloon and aligns the micro syringe perpendicularly to the intestinal wall and, as the piston is released, drives the dissolvable needle into the wall. The microneedle dissolves within minutes and delivers its payload, while the balloon deflates, releases the carbon dioxide, and is excreted through the gastrointestinal tract (GI).

2.2 Summary of Prior Clinical Use/History

2.2.1 Non-Significant Risk Study

In a non-significant risk (NSR) study, a modified, needleless, medication-free version of the RaniPill™ Capsule was tested in 10 fasting and 10 postprandial healthy volunteers to examine the tolerability of the RaniPill™ Capsule ingestion, gastrointestinal progression, deployment and ultimate excretion of the device remnants, monitored with serial abdominal fluoroscopies. A single RaniPill™ Capsule was orally administered to each subject and radiographically tracked during its transit from the stomach to the small intestine. No adverse events were reported by the subjects in the study.

2.2.2 First-In-Human Study

This study was the first demonstration in humans (N=62) of the oral delivery of an injectable biotherapeutic via the orally ingestible RaniPill™ Capsule. This study suggested RaniPill™ Capsule may safely and effectively deliver a wide variety of biotherapeutics currently administered only via parenteral routes. Biotherapeutic was successfully delivered with a bioavailability of 65%. All devices were confirmed to have successfully been excreted by all subjects without sequelae. No serious or unexpected adverse events were observed during the transit of the RaniPill™ Capsule through the gastrointestinal tract.

2.3 Justification

In the previous studies, none of the participants reported any issues with swallowing the RaniPill™ Capsule. These studies were conducted in young healthy volunteers. The goal of the present study is to enroll patients of different age groups who are taking injections and will be potential candidates for the RaniPill™ Capsule when it becomes available. Understanding patient treatment preference is important in early drug development. Collecting data on patient preference of new and current therapies may help inform the benefit-risk assessment of the product (**Bouvy 2020**). The ease of swallowing oral drug therapy is a key determinant for patient acceptability. The European Medicines Agency (EMA) in 2017 released a reflection paper regarding pharmaceutical development of medicines for use in older populations and suggested swallowability and palatability are key characteristics for patient acceptability (**EMA 2017**). Ternik, et al., conducted a workshop dedicated to acceptability assessments for pediatric pharmaceutical products with similar conclusion of swallowability and palatability contributing to oral drug acceptability in pediatric patients (**Ternik 2018**). Swallowability and palatability ratings of new oral drug therapies may drive patient selection to new oral therapies vs their current injection options.

The study will test the swallowability of a pill similar in shape and size to the RaniPill™ Capsule to be referred to as Mock-RP.

3 INTENDED USE, INDICATIONS FOR USE AND PRODUCT DESCRIPTION

3.1 Intended Use

The Mock-RP is not intended to deliver a treatment for a disease.

3.2 Proposed Indication for Use

The Mock-RP will not be used to treat disease in participants.

3.3 Investigational Clinical Trial Material (CTM) Description

In this study, a Mock-RP capsule shell, similar to weight, shape and size of the RaniPill™ Capsule, will be filled with potato starch, enteric-coated with colorant and lubricous coating (**Figure 1**).

Figure 1: Enteric-coated Capsule

The potato starch is considered natural and produced directly from a peeled, ground, washed and dried potato. The Mock-RP is an investigational CTM and will be manufactured by Rani Therapeutics. The Mock-RP will not contain a needle or drug and will be packaged and labeled individually in a plastic vial with a snap on cap. The Mock-RP will be delivered directly to the investigator by the sponsor's representative and stored at room temperature under standard security protocols.

4 METHODOLOGY AND ENDPOINTS

The objective of this study is to assess a participant's ability to swallow a Mock-RP.

Eligible participants will complete a questionnaire to assess their experience on an alternative therapy in pill form. Upon completion of the questionnaire, participants will be requested to swallow a Mock-RP then complete a questionnaire assessing a participant's ability to swallow the Mock-RP. Anticipated participant duration is approximately 1 hour.

4.1 Study Endpoints

Several endpoints will be evaluated, including:

- Percent of participants successfully swallowing the Mock-RP as reported on the questionnaire.
- Assess if participant would choose a pill instead of their current injection therapy if a pill becomes available.
- Participant experience with swallowing Mock-RP stratified by number of years using injections.
- Participant experience with swallowing Mock-RP stratified by age (21-50, 51-65, 66-75 years).
- Participant experience with swallowing Mock-RP stratified by frequency of injection treatment.
- All adverse events categorized by type and frequency.

4.2 Minimization of Bias

Potential sources of bias in this study may result from selection of participants, treatment of participants, and evaluation of study data. The following methods have been incorporated into the study protocol to minimize potential bias:

- Participants will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to Mock-RP swallowing attempt.
- All Site and Sponsor personnel will be trained on their respective aspects of the study using standardized training materials.
- All study personnel will be trained on and required to follow the CIP.
- All study investigators will be required to provide Financial Disclosure.
- Rani Therapeutics will monitor the investigation for adherence to GCP the CIP and accurate data reporting.

5 STUDY SAMPLE SIZE

As a prospective, single-center, open-label, single-arm, observational study, no statistical criteria for sample size are required. A total of 30 to 50 participants in each age group (21-50, 51-65, 66-75), for a total of up to 150 participants will provide sufficient data to characterize the endpoints, as well to evaluate swallowing trends between subgroups.

6 STUDY SITE INFORMATION

6.1 Agreements

Rani Therapeutics will sign a Clinical Trial Agreement (CTA) between Rani Therapeutics and the principal investigator (PI) and/or investigative site. This agreement will outline the financial and contractual arrangements between the parties.

6.2 Institutional Review Board (IRB)

IRB approval of the current CIP, Informed Consent Form (ICF), and any other study materials provided to prospective participants is required prior to enrolling any participants. Recruitment materials must be approved by the IRB before their presentation to prospective participants. Continuing review is required throughout the duration of the study until the time of study closure.

6.3 Investigator Responsibilities

Before participating in the study, all Investigators must agree to respect and fulfill the terms of this Investigational Plan.

- The investigator is responsible for ensuring this study is conducted according to the signed agreements, this CIP, all applicable regulations, and any conditions imposed by the IRB.

- The investigator is responsible for obtaining the written and dated approval/favorable opinion of the IRB for the clinical investigation before obtaining informed consent or allowing any participant to participate.
- The investigator is responsible for ensuring all IRB policies and procedures are followed.
- The investigator is responsible for protecting the rights, safety, and welfare of participants under the investigator's control.
- The investigator is responsible for obtaining informed consent.
- The investigator must document and explain any deviation from this CIP.
- The investigator is responsible for control of study CTM in his or her facility and must ensure they are only used by authorized persons for participants in this study and must ensure they are returned to Rani Therapeutics when requested.
- An investigator must disclose sufficient conflicts of interest, including financial information. The investigator must promptly update the information if any relevant changes occur throughout the study and for one year following study closure.
- The investigator must maintain a list of appropriately qualified persons to whom the investigator has delegated study activities. This document is referred to as the Delegation of Authority Log for this study. Even though tasks may be delegated, the investigator is ultimately responsible for the conduct of the study at his or her institution. The investigator must not allow persons on the delegation log to perform study activities until they are trained by the Rani Therapeutics study team.
- The investigator must have sufficient time and resources to properly conduct and complete the study.
- The investigator must maintain accurate and complete records relating to the investigation.
- The investigator must be responsible for all study related medical decisions and ensure that adequate medical care is provided to a participant for adverse events.

The investigator should ensure the accuracy, completeness, and timeliness of all data and reports submitted to Rani Therapeutics and the IRB.

6.4 Sponsor Responsibilities

The Sponsor responsibilities include, but are not limited to:

- Selecting appropriately qualified principal investigators.
- Providing investigators with the information they need to conduct the investigation properly.
- Ensuring proper monitoring of the investigation.

- Securing compliance and maintain records to document the compliance of all parties involved in the clinical investigation.

Rani Therapeutics and industry personnel can provide technical support to the Investigator and other health care personnel (collectively HCP) as needed during testing required by the protocol and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the procedures and forms related to the protocol.

In addition, Rani Therapeutics may perform certain activities to ensure study quality. These activities may include:

- Observing testing to provide information relevant to protocol compliance.
- Reviewing collected data and study documentation for completeness and accuracy.

Rani Therapeutics will not:

- Practice medicine.
- Provide medical diagnosis or treatment to participants.
- Discuss a participant's condition or treatment with a participant without the approval and presence of the HCP.
- Independently collect critical study data.
- Enter data in electronic data capture systems.

6.5 Study Training

Persons who conduct study activities under this CIP must be trained prior to performing study activities. The site PI must be trained before the site may be activated. PIs will be trained on the following:

- CIP, including but not limited to visit procedures, informed consent, investigator responsibilities, investigational CTM usage and handling, data collection, electronic data capture system, adverse events, reporting requirements, participant withdrawal, and study deviations.
- ICH Guideline on Good Clinical Practices (GCP) E6, Section 4, Investigator
- Investigator responsibilities described in 21 CRF 312 Subpart D

All other site and sponsor personnel who perform study activities must be trained on study activities relevant to their roles and responsibilities.

6.6 Site Selection

Sites will be selected based on research infrastructure, the availability of the potential participant pool that meets study inclusion criteria, and the site's ability to perform the research in compliance with the CIP.

6.7 Site Activation

Site activation is defined as the point in time where the sponsor notifies the PI in writing that the study may begin, and participants may be consented (enrolled) at his or her site. All local regulatory requirements must be fulfilled before the site can be activated. Rani Therapeutics will provide each PI written notification upon site activation. The following must be complete and received by Rani Therapeutics prior to a site's activation:

- Financial Disclosure Form: The PI must disclose any financial arrangements he or she has with Rani Therapeutics that meet the following requirements per 21CFR54:
    - Payment to the PI that could be influenced by the outcome of the trial
    - Any other significant payments (≥ $25,000), such as research grants, consulting, etc.
    - Any proprietary interest in the investigational CTM
    - Any significant equity interest in Rani Therapeutics (≥ $25,000)
- Confirmation that PI has completed study training
- IRB approval of the CIP
- IRB approved ICF
- Current Curriculum Vitae (CV) of the PI
- Fully executed CTA between Rani Therapeutics and the PI and/or Institution

Other study site personnel, including sub-investigators, may not participate in study activities until compliance with all individual requirements are documented.

The following must be completed before individual site personnel may perform study activities:

- Site activation must be complete (the PI must have all aforementioned items completed)
- Training pertinent to the individual's role
- Individuals must be named on the list of appropriately qualified persons to whom the investigator has delegated significant study-related duties
- Current CV (for sub-investigators only)
- Financial Disclosure Form (for sub-investigators only)

7 STUDY DESIGN

This is a prospective, single-center, open-label, single-arm, observational study assessing participant experience with swallowing the Mock-RP.

7.1 Participant Selection

Participants ≥21 years old who are currently taking injections to treat chronic disorders (e.g., diabetes (I or II), rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylolisthesis, psoriasis, growth hormone deficiency, hemophilia A) will be enrolled.

7.2 Study Inclusion and Exclusion Criteria

Upon confirmation that a consented participant meets all inclusion criteria and none of the exclusion criteria, the participant is considered eligible for randomization, and the study procedure can be scheduled.

7.2.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all the following criteria:

1. Participant age is 21 – 75 years
2. Participant understands the nature of the study, is willing to comply with protocol defined evaluations, and provide written informed consent
3. Participant currently taking injections to treat a chronic disorder
4. Non-pregnant, non-lactating female
   NOTE: Females who are of childbearing potential must have had a negative pregnancy test on day of screening

7.2.2 Exclusion Criteria

Individuals eligible to participate in this study must not meet any of the following criteria:

1. Active case of COVID-19
2. History of Dysphagia
3. History of dementia (e.g., Alzheimer's, vascular dementia, dementia with Lewy bodies, etc.)
4. Participant self-reports issues with swallowing pills.
5. History of drug or alcohol abuse or any other factor that, in the Investigator's opinion, may interfere with the participant's ability to cooperate and comply with the study procedures
6. History of allergic reaction to a component of the Mock-RP
7. History which, in the investigator's judgement, makes the participant ineligible or exposes the participant to unacceptable risks

7.3 Enrollment

Up to 200 men and women volunteers age ≥21 currently using injection therapy will be recruited from the general population and enrolled (consented) and up to 150 participants will attempt to swallow the Mock-RP after passing protocol required screening. A total of 30 to 50 participants will be included in each of the following age (years) groups: 21-50, 51-65, 66-75. Participants must meet all inclusion and none of the exclusion criteria prior to swallowing the Mock-RP.

7.4 Informed Consent Process

Informed Consent is a legally effective, documented confirmation of a participant's voluntary agreement to participate in a clinical investigation after the information has been given to the participant on all aspects of the clinical investigation that are relevant to the participant's decision to participate. The ICF will be approved by an IRB prior to the commencement of the clinical investigation at an investigative site. Any changes to the ICF must be approved by the IRB

reviewing the application before being used to consent a prospective study participant. It is recommended, but not required, that changes made to the ICF be submitted to Rani Therapeutics for review prior to being used to consent a prospective study participant. The current IRB approved version of the ICF must be used. Participants must provide informed consent prior to any study-related procedures.

The process of obtaining a participant's informed consent will:

- Ensure that the PI or his/her authorized designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the participant's decision to participate throughout the clinical investigation
- Provide opportunity for participant to ask questions
- Avoid any coercion or undue improper influence on, or inducement of, the participant to participate
- Not waive or appear to waive participant's legal rights
- Use native language that is non-technical and understandable to the participant
- Provide ample time for the participant to read and understand the informed consent form and to consider participation in the clinical investigation
- Ensure participant, or an authorized designee responsible for conducting the informed consent process, dates and signs the ICF. The investigator and research staff cannot sign or date the ICF for the participant.
- The original signed and dated ICF and documentation of the consent process must be retained at the investigative site and available for monitoring and auditing.
- Show how informed consent is obtained and recorded in special circumstances (e.g., participant needing legally designated representatives, participant unable to read or write) where the participant is unable to provide it
- A copy of the signed and dated ICF (and data privacy language where required by law) must be provided to the participant (or person who signed the form in the case of a legally authorized representative).
- Data protection authorization/or other privacy language needs to be collected where required by law or local regulation.
- If using an electronic ICF, there needs to be a documented electronic signature process which is in compliance with applicable regulations (refer to 21 CRF part 11).
- It is recommended that the informed consent process is documented in the participant's medical records.

Any new information should be provided to the participant if it could affect the participant's willingness to participate.

7.4.1 Protection of Participant Data

The Sponsor and any designated CROs will make every reasonable effort to protect the confidentiality of the participants participating in the study. Except as required by law, participants will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. A unique identification code will be assigned to each participant participating in this study. Information about the code will be kept in a secure location by the Investigator. All participant data will be stored in locked offices. All electronic data will be password-protected on computers stored in locked offices. Access to participant information will be limited to study personnel only. Any data, including photographs, that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique participant code and will not reveal the participant's identity without the express approval of the participant. It is possible that participant personal health records may be disclosed to other agencies such as regulatory bodies as per country regulations.

Data storage will reside at the clinical research sites and at Rani Therapeutics. Sites will retain data collected during the clinical trial for a minimum of 15 years. Sponsor will retain data per company Standard Operating Procedures.

The HIPAA requirements affect clinical trials in three key areas as described below:

- **Accounting of Disclosures:** Data collected during the conduction of prescreening activities for this clinical trial are participant to the HIPAA accounting of disclosures' regulations. It is the responsibility of the investigative center to tell all participants whose records were screened for eligibility in the trial that their records were used in this manner if he or she requests an accounting of when his or her data were disclosed.
- **Consent:** All participants in the clinical trial will be made aware that their participation in the clinical trial will involve disclosure of certain protected health information to Rani Therapeutics and for what purpose. The Informed Consent form will contain a listing of the type of information that will be disclosed during the clinical trial.
- **Withdrawal of Consent:** HIPAA specifically allows companies such as Rani Therapeutics participant to jurisdiction of the FDA access to protected health information for activities related to the quality, safety or effectiveness of devices. This means that Rani Therapeutics can use data from this clinical trial even if the individual withdraws his or her authorization.

7.5 Participant Accountability

Following completion of screening, participants will be assigned to their age group and have one study visit to swallow the Mock-RP and complete questionnaires (**Figure 2**).

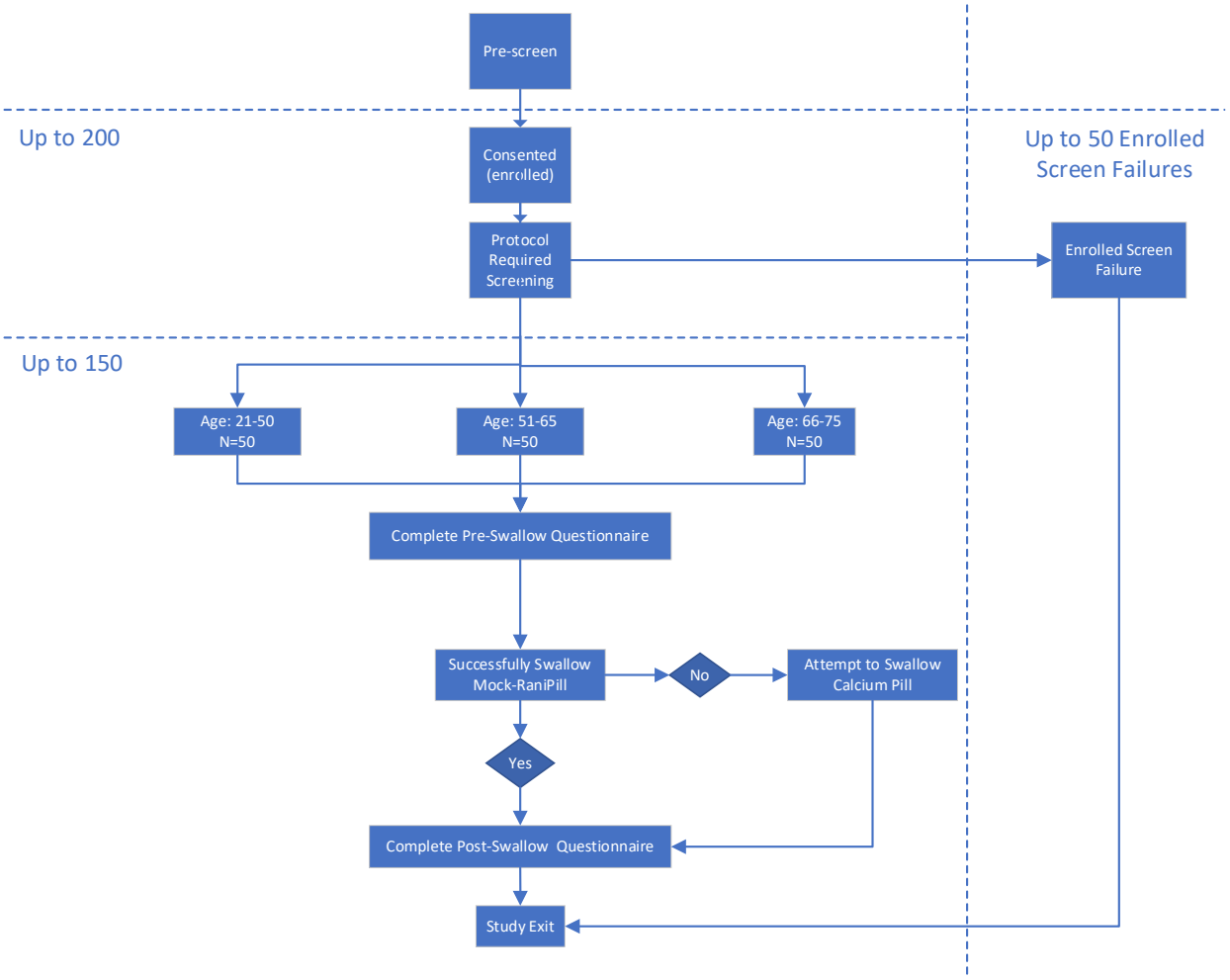

Figure 2: Participant Accountability Overview

Screening and visit requirements are outlined in Table 1.

Table 1: Screening and Visit Requirements

	Swallow Visit
Inclusion/Exclusion criteria review	√
Informed Consent	√
Medical Hx/Demographics	√
Weight/Height/Temperature	√
Concomitant Medications	√
Urine Pregnancy Test	√^
Dispense Mock-RP	√
Questionnaires	√
Dispense Calcium Pill, if necessary	√*
Adverse Event(s)	√

^ Pregnancy test completed on day of screening.
* Dispense ONLY if participant is unable to swallow the Mock-RP

7.6 Screening Procedures

All participants currently using injections at each participating investigational site should be evaluated for study eligibility. Participants may be recruited from clinical site databases, general population, using flyers, broadcast or web-based/social media. For participants who appear to meet study criteria, the Investigator (or designee) will discuss the study with the potential participant and ask him/her to consider study participation. Along with other required elements, the background and purpose of the study, participation requirements, the potential benefits and risks of participation must be explained to the participant. If he/she agree, an Informed Consent Form (ICF) must be signed to document the consenting process. Prior to any non-standard-of-care procedures, the participant must sign the Informed Consent Form approved for use by the IRB. Participants must be provided a copy of the signed ICF for their reference.

7.6.1 Pill Swallowing Issues

Participants will report if they have issues swallowing pills.

7.6.2 Clinical Examination

A medical history focusing on, but not limited to, the 90 days before study day will be obtained. The history will review the use of medications, including prescription and non-prescription pharmaceuticals per Section 7.6.3 “Concomitant Medications, Treatments, and Procedures”.

Height, weight, and temperature will be measured before administration of the Mock-RP capsule.

7.6.3 Concomitant Medications, Treatments, and Procedures

The concomitant prescription and non-prescription pharmaceuticals must be reported in the CRF at screening. For this protocol, a prescription medication is defined as one that can be prescribed only by a licensed physician.

7.6.4 Urine Collection for Pregnancy

In women of childbearing potential, urine pregnancy tests will be performed the day of the study. Pregnancy tests are not required for surgically sterile or postmenopausal women. Tests will be performed on-site and results must be known before administration of the study CTM.

7.7 Visit Procedures

7.7.1 Pre-Swallow Questionnaire

Participant will complete the pre-swallow questionnaire to self-report any historical issues with swallowing pills, current medicines they take in pill form, and if they would take an alternative therapy in pill form.

7.7.2 Mock-RP Swallowing

The participant should rinse their mouth with water before swallowing the Mock-RP then swallow the pill the way they always swallow pills, without chewing. While swallowing, the participant should take into account how the pill feels on the surface of their tongue and palate.

7.7.3 Post-Swallow Questionnaire

Participant should complete the post-swallow questionnaire to report the palatability and swallowability of the Mock-RP.

7.7.4 Calcium Pill Swallowing, if necessary

Participants unable to swallow the Mock-RP on the post-swallow questionnaire (responded “No” to “Did you manage to swallow the pill?”) will be asked to attempt to swallow a Calcium dietary supplement (Rapid Release Calcium in Liquid Softgel – contains 600 mg calcium as calcium carbonate per softgel and 500IU Vitamin D as D3 Cholecalciferol per softgel). The participant should rinse their mouth with water before attempting to swallow the calcium pill then swallow the pill the way they always swallow pills, without chewing.

7.7.5 Unscheduled Visits

Participant study duration will be approximately 1-hour; thus, no unscheduled visits are anticipated in this study.

7.7.6 Participant Withdrawal Criteria

Participants can withdraw from the study at any time for any reason; the reason for withdrawal will be documented. All data available at the time of withdrawal (if any) will be used for analysis. There will be no further data collection per this study Investigation Plan on the participant who has withdrawn.

8 INVESTIGATIONAL CTM HANDLING AND TRACEABILITY

The Mock-RP is investigational and will be tracked from the time it is shipped and/or hand carried from Rani Therapeutics until it is either used in the study or returned to the sponsor. A CTM

Accountability Log will be maintained at each study site and will be provided by Rani Therapeutics in the Regulatory Binder. CTM allocated for site use will be recorded in the CTM Accountability Log upon delivery to the study site and will be stored in a secured area until use. The log should include:

- name(s) of person(s) who received used, returned, or disposed of the CTM
- The date of receipt, identification, and quantity of each CTM
- The expiry date, if applicable
- The date of use
- Participant identification
- The date of return of unused or expired CTM, if appliable
- The date and documentation of disposal of the CTM as per instructions of the sponsor, if applicable.

All unused study CTM must be returned to Rani Therapeutics.

9 STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the protocol or the CTA. Prior approval by Rani Therapeutics and IRB is expected in situations where the investigator anticipates, contemplates, or wishes to make a conscious decision to deviate if the deviation affects participant's rights, safety, and well-being, or the scientific integrity of the clinical investigation. Prior approval is not required when a deviation is necessary to protect the life or physical well-being of a participant in an emergency or in unforeseen situations beyond the investigator's control (e.g., participant failure to attend scheduled follow-up visits, inadvertent loss of data due to a computer malfunction, etc.). All study deviations must be reported regardless of whether medically justifiable, pre-approved by Rani Therapeutics, an inadvertent occurrence, or done to protect the participant in an emergency. The deviation must be recorded and documented in participant medical/research record with an explanation for the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or regulatory agency requirements, if applicable.

The PI shall notify Rani Therapeutics and the reviewing IRB of any deviation from this CIP affecting the participant's rights, safety, and well-being of human participants under emergency circumstances. Notification must be given as soon as possible, but in no later than 5 working days after the emergency occurred. Rani Therapeutics is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the CIP, conduct additional training, etc.). Repetitive or serious investigator compliance issues may require initiation of a corrective action plan with the investigator, and in some cases, necessitate suspending site enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

10 ADVERSE EVENTS DEFINITIONS AND REPORTING

10.1 Adverse Event

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons whether or not related to the investigational CTM.

10.2 Serious Adverse Events (SAE)

An adverse event is considered serious when it:

- Led to death,
- Led to serious deterioration in the health of the participant, that either resulted in
  - A life-threatening illness or injury, or
  - Permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

All SAEs will be reported on the SAE report form.

10.3 Unanticipated Problems

Any unexpected, serious adverse effect on health or safety of participants having implications for the conduct of the study (e.g., requiring a significant and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure) not previously identified in nature, severity, or degree of incidence in the study protocol, informed consent or investigator's brochure.

10.4 Adverse Event Relatedness

The clinician's assessment of an AE's relationship to the study CTM is part of the documentation process, though does not determine whether it is reported. Clinical observations suspected to be an AE must be reported. For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and clinical judgment. The degree of certainty of causality will be graded as:

- **Definitely Related**: There is unequivocal evidence of a causal relationship, and other possible contributing factors can be ruled out. The timing of a clinical event, including an abnormal laboratory test result, is related to the delivery of the study CTM and is not explained by a concurrent disease or other pharmaceuticals or chemicals. The response to withdrawal of the study CTM (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive. The AE is expected to be reproduced by an appropriate re-challenge procedure.

- **Probably Related**: There is evidence of a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after the administration of the study CTM, is unlikely to be due to a concurrent disease or other pharmaceuticals or chemicals, and responds as expected to a de-challenge.
- **Possibly Related**: There is some evidence in favor of a causal relationship (e.g., the event occurred within a reasonable time after administration of the study CTM), though other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may be listed as "possibly related" soon after its identification, it may be flagged as requiring more information and later upgraded to "probably" or "definitely" related, as appropriate.
- **Probably Not Related**: A clinical event, including an abnormal laboratory test result, whose temporal relationship to the study CTM administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study CTM) and where other pharmaceuticals or chemicals, or an underlying disease provide a satisfactory explanation (e.g., the participant's clinical status, a concomitant treatment).
- **Unrelated**: The AE is completely independent of the administration of the study CTM, or the event is unequivocally due to another cause. There must be an alternate, definitive cause documented by the clinician.

10.5 Adverse Event Severity

Adverse event severity will be categorized using the following definitions:

- **Mild**: Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate**: Events result in minor inconvenience or concern with the therapy. Moderate events may interfere with some functions.
- **Severe**: Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events may be life-threatening or incapacitating.

10.6 Deaths

During the study, all deaths must be reported to Rani Therapeutics within 24 hours. A copy of the participant's death records, medical records for the events that led to the participant's death, and a death certificate (if available) should be provided.

10.7 Anticipated Adverse Events

Known potential risks of swallowing the Mock-RP include:

- Oropharyngeal symptoms (coughing, gagging, etc.)

- Airway obstruction due to accidental aspiration
- Dysphagia
- Nausea/vomiting
- Dyspepsia

10.8 Adverse Event Reporting

All adverse events occurring from the start of any study specific screening procedures must be recorded in the eCRF. Adverse events identified and reported in this study will be classified in accordance with the adverse event diagnosis and reported to the IRB per local requirements.

AEs must be recorded on the eCRF and be described by (a) duration (start and resolution dates); (b) signs and symptoms; (c) final event diagnosis; (d) event severity; (e) Investigator's clinical opinion on the relationship to the study CTM; (f) action taken to resolve the event; (g) outcome of the event; and (h) whether or not such event is considered to have been serious and/or unanticipated.

Adverse events should be reported according to their underlying cause, if known. Multiple symptoms related to a single diagnosis should not be reported as separate AEs. Only concomitant AEs that are unrelated to each other (in the clinician's judgment) should be reported as separate events.

11 BENEFIT-RISK ANALYSIS

The use of the Mock-RP may be associated with adverse effects; however, in this pill swallow study, the overall and serious adverse effect risks are anticipated to be low and very low, respectively. Most adverse effects, if any, are likely to occur during swallowing of the Mock-RP.

11.1 Potential Risks

There are risks to the participant associated with study participation. Risks are associated with administration of the Mock-RP (defined in section 10.7) and participation in a clinical study. The greatest risk of participating in this clinical study is loss of confidentiality. Every attempt will be made to ensure participant confidentiality.

11.2 Potential Benefits

There are no anticipated benefits from participation in this study other than free medical tests. Future clinical use of the RaniPill™ Capsule is likely to improve participants' quality of life and increase their compliance with treatment by offering a needle-free alternative to repeated injections.

12 EARLY TERMINATION

Rani Therapeutics may terminate Investigator and/or site participation in the study for issues including but not limited to the following:

- Evidence of an Investigator's failure to maintain adequate clinical standards
- Evidence of an Investigator or staff's failure to comply with the CIP
- Inaccuracy or late submission of data forms
- Conditions of approval imposed by the reviewing IRB
- Evidence of safety concerns
- Change of staff at site that adversely impacts study conduct

Any evident pattern of non-compliance with respect to these standards will have corrective actions implemented. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw from the study and their site may be replaced.

If Rani Therapeutics terminates or prematurely suspends the study, the investigators will be promptly informed of the rationale. In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB. In the case of study termination, the investigator must inform the participants.

If the investigator terminates or suspends the study without the prior agreement of Rani Therapeutics, the investigator will promptly inform Rani Therapeutics and provide a detailed written explanation of the termination or suspension. The investigator will promptly inform the institution (where required per regulatory or local requirements), the IRB, and the participants.

If the IRB terminates or suspends its approval of the study, the investigator will promptly inform Rani Therapeutics and provide a detailed written explanation of the termination or suspension. Participant enrollment must stop at the site until the IRB suspension is lifted. The investigator will inform his/her institution (where required per regulatory or local requirements). The investigator will promptly inform the participants of the rationale for the study termination or suspension.

13 STATISTICAL METHODS

Categorical data will be summarized using frequency tables, presenting the participant counts and relative percentages. Continuous variables will be summarized by the mean, standard deviation, median, minimum and maximum. The SAS system or equivalent statistical package will be used to perform all analyses. Exact confidence intervals will be generated for estimates of proportions. Asymptotic confidence intervals will be generated for estimates of means. Except where otherwise noted, p-values of all tests will be reported without any correction for the multiplicity of tests performed.

13.1 Analysis Cohorts

All participants who attempt to swallow the Mock-RP in the study are included in the Analysis Cohort used for evaluating swallowability of the Mock-RP.

13.2 Sample Size Justification

As an observational study, no hypothesis tests are planned. All data will be summarized. Nevertheless, with the sample size proposed for the study, the following levels of precision of the estimates, expressed as the width of the confidence interval, can be achieved:

1. The width of the exact 95% two-sided confidence interval for percentages will be no wider than +/- 14.5% with 50 participants contributing to the estimate of the proportion and will be no wider than +/- 8.3% with 150 participants.
2. The width of the 95% two-sided confidence interval for the mean will be equal to +/- 27.7% of the standard deviation with 50 participants contributing to the estimate of the mean and will be equal to +/- 16.0% of the standard deviation with 200 participants.

14 DATA AND QUALITY MANAGEMENT

All information and data sent to Rani Therapeutics concerning participants or their participation in this study will be considered confidential. All data used in the analysis and reporting of this clinical study will be used in a manner without identifiable reference to the participant. The investigator consents to visits by Rani Therapeutics staff, contractors, and authorized governmental bodies to review the study participants' medical records, including any test or laboratory data that might have been recorded on diagnostic test media.

Data will be stored in a secure, password-protected database. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, and any potential interim analysis, data will be frozen and retained by Rani Therapeutics. Procedures for data review, database cleaning, issuing and resolving data queries, verification, validation and securing of electronic clinical data systems, and data retention will be documented separately.

14.1 Electronic Case Report Forms

All required clinical data for this study will be collected in web-based standardized eCRFs. Participant IDs and initials (where allowed) will be used to track participant information throughout the study. The study database will be developed and maintained according to written procedures and will be compliant with signature requirements in 21 CFR 11.

To facilitate transcription into the eCRFs, worksheets may be provided to the investigational sites.

15 AMENDMENTS TO THE PROTOCOL

The study sponsor may request that the investigator submit an amendment to the protocol for IRB review if the sponsor proposes a change in the protocol that may affect its scientific soundness or the rights, safety, or welfare of participants. These amendments must be approved by the IRB before implementation.

16 MONITORING, AUDITING AND INSPECTING

16.1 Monitoring Plan

During the course of the study, the sponsor will maintain regular contact with the investigative sites and monitor (e.g., central monitoring, on-site monitoring visits, and source data verification) on a regular basis to ensure compliance with this study protocol. Monitoring will be performed according to specific predefined monitoring Standard Operating Procedures (SOPs) and a study specific Monitoring Plan to ensure that the Investigator and his/her study team conduct the clinical investigation in accordance with the signed Clinical Trial Agreement, the CIP, any conditions imposed by the IRB, the Declaration of Helsinki, 21 CFR Parts 50, Good Clinical Practice according to ICH E6, and any other applicable regulations, to ensure adequate protection of the rights and safety of participants and the quality and integrity of the resulting data. Monitoring visits will be documented using monitoring visit reports. Rani Therapeutics must, therefore, be allowed access to the participant's clinic and hospital records when so requested as per the participant informed consent document, Privacy Authorization, and CTA.

The primary focus of the monitoring visits will be on the processes critical to protecting human participants, maintaining the integrity of study data, and compliance with applicable regulations. The findings will be used to correct investigator and site practices that could result in inadequate human participant protection and/or poor data quality.

16.2 Access to Study Records

The PI and site personnel must permit study-related monitoring, audits and IRB review by providing direct access to source documents. The PI should be available to the clinical study team to discuss the results of monitoring visits. Access to participant records (including hospital and clinic records) and regulatory documents must be granted to the Sponsor's monitors.

17 REQUIRED RECORDS AND REPORTS

Investigators and Rani Therapeutics shall maintain records for this study for a period of at least 2 years after the date on which the investigation is terminated or completed. An investigator may withdraw from the responsibility to maintain records for this period and transfer custody of the records to any other person who will accept responsibility for them.

17.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All the below records, with the exception of case history records and electronic case report forms,

should be retained. Electronic case report forms (eCRFs) may be maintained and signed electronically within the electronic data capture system during the study.

- All correspondence between the IRB, Sponsor, another investigator, monitor and/or the investigator that pertains to the investigation, including required reports
- Participant's case history records, including, but not limited to:
  - Signed and dated informed consent form
  - Signed and dated privacy authorization form (may be combined with the informed consent form)
  - Observations of adverse events/adverse device effects
  - Medical history
  - Procedure and follow-up data
  - Documentation of the dates and rationale for any deviation from the protocol
- Signed and dated eCRFs
- Investigational CTM traceability records
- All approved versions of the CIP and IB
- Signed and dated CTA
- Investigator's current CV
- Delegation of Authority Log
- IRB study approval documentation, including written confirmation that the investigator or other study staff, if a member of the IRB, did not participate in the approval process

17.2 Investigator Reports

The investigator shall prepare and submit in a complete, accurate, and timely manner, the reports listed in Table 2.

Table 2: Investigator Reporting Requirements

Report	Submit to:	Description/Constraints
Unanticipated Problems	Sponsor	Report to Sponsor ASAP, but no later than 72 hours after the investigator first learns of the effect
	IRB	Report per the IRB policies and procedures
Withdrawal of IRB approval	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB
Study CTM Related SAE	Sponsor	Report to Sponsor ASAP, but no later than 72 hours after the investigator first learns of the effect
	IRB	Report per the IRB policies and procedures
Deviations from the CIP	Sponsor and IRB	An investigator must notify the sponsor and IRB of any deviation from the CIP to protect the life or physical well-being of a participant in an emergency. Such notice shall be given ASAP, but no later than 5 working days after the emergency occurred

Report	Submit to:	Description/Constraints
Failure to obtain informed consent prior to study CTM administration.	Sponsor and IRB	If an investigator uses study CTM without obtaining informed consent, the investigator shall report such use within 5 working days after device use
Final report	Sponsor	This report must be submitted within three months of study completion or termination of the investigation or the investigator's part of the investigation
Progress	Sponsor and IRB	An investigator shall submit progress reports to the sponsor and IRB at regular intervals, but in no event less often than yearly
Death	Sponsor	Within 10 days of knowledge of death

17.3 Sponsor Records

Rani Therapeutics will maintain the following accurate, complete, and current records relating to this investigation:

- All correspondence with an investigator or an IRB, including required reports.
- Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type, and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any study CTM returned to Rani Therapeutics or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.
- Signed financial disclosure information.
- Records concerning adverse events.

17.4 Sponsor Reports

Sponsor reporting requirements are outlined in Table 3.

Table 3: Sponsor Reporting Requirements

Report	Submit to:	Description/Constraints
Unanticipated Problems Evaluations	All participating investigators	10 working days after the sponsor first receives notice of the effect.
Withdrawal of IRB approval	All reviewing IRB, and participating investigators	Within 5 working days after receipt of notice of the withdrawal of approval
Progress Reports	IRB and participating investigators	At regular intervals, at least yearly
Recall and device disposition	All reviewing IRB and participating investigators	Any request that an investigator return or otherwise dispose of any unit of a study CTM shall be reported within 30 working days after the request is made and shall state why the request was made
Final Report	All reviewing IRB and participating investigators	Within 6 months of study termination

18 PUBLICATIONS

Study results will be published following the final study analyses. The International Committee of Medical Journal Editors (ICMJE) authorship guidelines will be used. The ICMJE guidelines require the conditions below are met to be included as an author:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

This study will be registered in www.clinicaltrials.gov, and results will be posted.

19 REFERENCES

1. Bouvy, JC., Cowie, L., Lovett, R., Morrison, D., Livingstone, H., Crabb, N., Use of patient preference studies in HTA decision making: A NICE perspective. *The Patient-Patient-Centered Outcomes Research*. 2020;13,145-149.
2. European Medicines Agency, 2017. Reflection paper on the pharmaceutical development of medicines for use in the older population, EMA/CHMP/QWP/292439/2017.
3. Ternik, R., Liu, F., Bartlett, J., Khong, YM., Thiam Tan, DC., Dixit, T., Wang, S., Galella, EA., Gao, Z., Klein, S., Assessment of swallowability and palatability of oral dosage forms in children: Report from an M-CERSI pediatric formulation workshop. *Int. J. of Pharmaceutics.,* 2018. 536; 570-581.