CLINICAL STUDY PROTOCOL

Comment [LN1]: Authors: There is a hidden text key for guidance text in this template.

Title: <<At a minimum, the title should identify the investigational product, the study design (e.g., parallel, cross-over, blinded, randomized), comparators (e.g. placebo, active, dose/response), patient population, and trial phase>>

Protocol Number:	<<Protocol Number>>
Investigational <<Drug or Device>>: Version:	<<Name of Product>> v. 0.0 (<<Date of Draft>>)
<<IND or IDE>> <<Applicant or Holder>>/Product Sponsor:	<<Name and Address of Applicant/Sponsor>> (If applicant is different from sponsor, these can be separated into different rows)
<< Device Manufacturer>>: (If applicable; otherwise delete this row)	<<Name and Address of Device Manufacturer>>
Authorized Signatory:	<<Name and Address of Person/Company Authorized to Sign Protocol and Amendments for the Sponsor>>
Study Contact:	<<Name, Title, and Telephone Number(s) of the Authorized Study Contact>>
<<Protocol Amendments>>: (If applicable; otherwise, delete this row)	<<Amendment Number>> <<Date>>

INVESTIGATOR'S SIGNATURE

I have received and read the investigator's brochure for <<Investigational Product>>. I have read protocol <<Protocol Number>> and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Title of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR'S SIGNATURE

Approved by:

<<Name of Sponsor Authorized Signatory>>	Date
<<Title>>	
<<Sponsor Company>>	

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	<<Name>>	<<Name of Company, Address, and Contact Number(s)>>
Responsible Physician	<<Name of Medical Expert/Monitor for the Trial>>	<<Name of Company, Address, and Contact Number(s)>>
<<Drug or Device>> Safety Physician	<<Name of Medical Expert/Monitor for Safety>>	<<Name of Company, Address, and Contact Number(s)>>
<<24-hour>> Emergency Contact	<<Name of Medical Expert/Monitor for the Trial>>	<<Name of Company, Address, and Contact Number(s)>>

(If an individual is designated for multiple roles, these rows can be edited or combined as applicable.)

Comment [LN2]: Authors: The Synopsis is included **only** for reference and is meant to be removed from this protocol template upon drafting.

1. SYNOPSIS

Protocol Title

<<Copy Title Verbatim from Title Page, Pg. 1>>

Protocol Number

<<Protocol Number>>

Clinical Phase

Phase <<2, 2/3, or 3>>

<<IND or IDE>> Applicant/Product Sponsor

<<Name of Applicant and Sponsor>> (If applicant is different from sponsor, these can be separate lines)

Device Manufacturer (if applicable)

<<Name of Device Manufacturer>>

Authorized Signatory

<<Name of Person/Company Authorized to Sign Protocol and Amendments for Sponsor>> (For a non-U.S. sponsor, the representative U.S. agent should also be specified)

Regulatory ID Number

<<Regulatory ID Number>>

Indication

<<Indication>>

Investigational <<Drug or Device>>

<<Name of Investigational Product>>

Control

<<Comparator(s) (e.g. placebo, active, dose/response)>>

Primary <<Efficacy (Drug/Biologic) or Effectiveness (Medical Device)>> Objective

<<A complete and specific, 1-2 sentence primary efficacy/effectiveness objective(s), which may include relevant treatments (e.g. investigational product and comparator(s)), clinical endpoint(s), duration of treatment/evaluation periods, etc.)>>

Secondary <<Efficacy or Effectiveness>> Objective

<<A complete and specific, 1-2 sentence secondary efficacy/effectiveness objective(s), which may include relevant treatments (e.g. investigational product and comparator(s)), clinical endpoint(s), duration of treatment/evaluation periods, etc.)>> (Alternatively, the secondary efficacy objectives can be combined into one section).

Safety Objective

<<A complete and specific, 1-2 sentence safety objective(s), which may include relevant treatments (e.g. investigational product and comparator(s)), clinical endpoint(s) (e.g. adverse events), the duration of treatment/evaluation periods, etc.>>

Primary <<Efficacy or Effectiveness>> Endpoint

<<Brief (approximately 1-3 paragraphs) description of the primary efficacy/effectiveness endpoint(s) for the study, which may include relevant treatments (e.g. investigational product and comparator(s)), outcomes measured, the duration of treatment/evaluation periods, reference to previous regulatory precedents, etc.>> (The primary efficacy/effectiveness endpoint(s) should directly address the objective(s))

Secondary <<Efficacy or Effectiveness>> Endpoint

<<Brief (approximately 1-3 paragraphs) description of the secondary efficacy/effectiveness endpoint(s) for the study, which may include relevant treatments (e.g. investigational product and comparator(s)), outcomes measured, the duration of treatment/evaluation periods, reference to previous regulatory precedents, etc.>> (The secondary efficacy/effectiveness endpoint(s) should directly address the objective(s))

Safety Endpoints

<<Brief (approximately 1-3 paragraphs) description of the safety endpoint(s) for the study, which may include relevant treatments (e.g. investigational product and comparator(s)), outcomes measured, the duration of treatment/evaluation periods, reference to previous regulatory precedents, etc.>> (The safety endpoint(s) should directly address the objective(s))

Investigational Products

Investigational <<Drug or Device>> Dosage

<<Dosage>> (If applicable)

Control Dosage

<<Dosage for control(s)>> (If applicable)

Study Population

Subject Selection Criteria

<<Include eligibility criteria, e.g. diagnoses and patient population, as well as key exclusion and key inclusion criteria for enrollment in the study>> (If applicable, detailed inclusion and exclusion criteria may be included in the section per Sponsor preference)

Study Overview/Design

<<A brief, 2-3 paragraph summary of the overall study design (including the type of trial conducted [e.g. double-blind, placebo- and/or active-controlled, parallel design], overall procedures and study stages), key trial endpoints. Include description of DSMB including role of DSMB in study execution, if applicable.>>

Statistics

Analysis Populations

<<A brief description of each subject population used in the statistical analyses should be included here>> (Example analysis populations are included below – Add to and/or modify with information applicable to the study)

Safety Population

<<1 sentence identification of safety population, e.g. all randomized subjects who receive at least one dose of study treatment>>

Intent-to-treat (ITT) Population

<<1 sentence identification of ITT population, e.g. all randomized subjects who receive at least one dose of study treatment and have at least X post-treatment visits>>

Per-protocol (PP) Population

<<1 sentence identification of PP population, e.g. all ITT subjects who have no major protocol deviations>>

Power and Sample Size

<<1-2 paragraph description of planned number of subjects (for each trial site, if applicable), randomization scheme (i.e. ratio of subjects randomized to investigational product versus comparator(s)), details on sample size calculations, planned statistical analyses (e.g. efficacy/effectiveness and safety analyses, screen failure/drop-out rate, etc.) and significance level, and subject populations included in the analyses>>

<<Efficacy or Effectiveness>> Analysis

Primary

<<Brief, 1-2 paragraph identification on primary efficacy/effectiveness analysis, including subject population(s), study endpoint(s), and general statistical approach (i.e. hypothesis and methods) used for analyses>>

Secondary

<<Brief, 1-2 paragraph identification on primary efficacy/effectiveness analysis, including subject population(s), study endpoint(s), and general statistical approach (i.e. hypothesis and methods) used for analyses>>

Safety Analysis

<<Brief, 1-2 paragraph identification on primary safety analysis, including subject population(s), study endpoint(s), and general statistical approach used for analyses>>

Pharmacokinetic Analysis

<<Brief, 1-2 sentences regarding the pharmacokinetic analysis, if applicable, including subject population(s), study endpoint(s), and general statistical approach used for analyses>>

TABLE OF CONTENTS

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No table of figures entries found. (If applicable)

LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Table 2: Abbreviations

Abbreviation or specialist term	Explanation
ADR	adverse drug reaction
AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
PP	per-protocol
Rho	Rho, Inc.
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
U.S.	United States

(Sample Table of Abbreviations – Add to and/or update with information applicable to the study)

2. INTRODUCTION

<<All relevant background information should be included here, e.g., 1) name and description of investigational product; 2) summary of clinically relevant findings from nonclinical/clinical studies; 3) summary of known and potential risks and benefits to human subjects; 4) justification of the study in the context of the overall clinical development plan; 5) description and justification of route of administration/dose/dose regimen/treatment period(s); 6) description of study population; 7) seminal references to literature and relevant data that provide background for the study>> (Note: this information is typically provided by the Sponsor; however, if Rho will author this section, the Sponsor should provide relevant references and guidance for rationale and development including at minimum the current Investigator's Brochure).

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

3. OBJECTIVES

3.1. Primary <<Efficacy or Effectiveness>> Objective(s)

<<Brief (approximately 1-3 sentences) description of the primary efficacy/effectiveness objective(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured, the duration of treatment/evaluation periods, etc.>>

<<NOTE: FDA commonly requires for device trials a separate discussion of "study success criterion" with respect to "clinical significance".>>

3.2. Secondary <<Efficacy or Effectiveness>> Objective(s)

<<Brief (approximately 1-3 sentences) description of the secondary efficacy/effectiveness objective(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured, the duration of treatment/evaluation periods, etc.>>

3.3. Safety Objective(s)

<<Brief (approximately 1-3 sentences) description of the safety objective(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured (e.g., adverse events), the duration of treatment/evaluation periods, etc.)>>

3.4. Additional Objective(s)

<<If applicable, brief (approximately 1-3 sentences) description of the additional objective(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured (e.g. pharmacokinetic parameters to determine the concentrations at steady state), the duration of treatment/evaluation periods, etc.)>>

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

<<An approximately 1-page description of the overall trial design, including at a minimum 1) a scientific statement of the primary and secondary endpoint(s) of the trial, as applicable; 2) a description of the type/design of the trial to be conducted (e.g., double-blind, placebo- and/or active-controlled, parallel design); and dose levels to be employed); key trial endpoints; and randomization/blinding schemes>> (A shorter, approximately 2-3 paragraph summary of the study design may be included in the Synopsis. Consider adding a schematic for complex study designs)

<<Include 1-2 sentences describing role of DSMB, if any, for this study. Describe frequency of meeting, role in decision making with respect to study execution. Cross-reference to a stand-alone Administrative Details section below, which provides additional details on DSMB composition and logistics.>>

4.2. Study Endpoints

4.2.1. Primary <<Efficacy or Effectiveness>> Endpoint(s)

<<Brief (approximately 1-3 paragraphs) description of the primary efficacy/effectiveness endpoint(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured, timepoints at which they are measured, the duration of treatment/evaluation periods, reference to previous regulatory precedents, etc.>> (The primary efficacy/effectiveness endpoint(s) should directly address the objective(s) in in Section 3.1)

4.2.2. Secondary <<Efficacy or Effectiveness>> Endpoint(s)

<<Brief (approximately 1-3 paragraphs) description of the secondary efficacy/effectiveness endpoint(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured, timepoints at which they are measured, the duration of treatment/evaluation periods, reference to previous regulatory precedents, etc.>> (The secondary efficacy/effectiveness endpoint(s) should directly address the objective(s) in in Section 3.2)

4.2.3. Safety Endpoint(s)

<<Brief (approximately 1-3 paragraphs) description of the safety endpoint(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured, timepoints at which they are measured, the duration of treatment/evaluation periods, reference to previous regulatory precedents, etc.>> (The safety endpoint(s) should directly address the objective(s) in Section 3.3)

4.2.4. Additional Endpoint(s)

<<Brief (approximately 1-3 paragraphs) description of the additional endpoint(s) for the study, which may include relevant treatments (e.g., investigational product and comparator(s)), outcomes measured, timepoints at which they are measured, the duration of treatment/evaluation periods, reference to previous regulatory precedents, etc.>> (The additional endpoint(s) should directly address the objective(s) in Section 3.4)

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible to enroll in the clinical trial:

<<List all of the inclusion criteria for trial eligibility via a numbered or bulleted list>>

5.2. Subject Exclusion Criteria

The presence of any of the following exclusion criteria excludes a subject from study enrollment:

<<List all of the exclusion criteria for trial eligibility via a numbered or bulleted list; note: exclusion criteria should not include the negative of any inclusion criteria.>>

5.3. Randomization <<Continuing Eligibility>> Criteria

<<if applicable to the study design>>Subjects who are enrolled into the <<Study Period/Phase/etc.>> will be evaluated for randomization eligibility at Study Visit X. Subjects must meet the following criteria to be randomized:

<<List all of the randomization criteria for trial eligibility via a numbered or bulleted list>>

5.4. Subject Withdrawal Criteria

<<Briefly discuss all of the subject withdrawal criteria (i.e., terminating investigational product/study treatment), typically in paragraph or list format, specifying: 1) when and how to withdraw subjects from the trial/investigational product treatment; 2) the type and timing of the data to be collected for withdrawn subjects; 3) whether and how subjects are replaced; 4) the follow-up procedures for subjects withdrawn from investigational product/study treatment >> (Example text is included below – Add to and/or update with information applicable to the study)

Subjects can withdraw consent at any time for any reason without effect on subsequent care. Subjects will be encouraged to adhere to the protocol and complete all required assessments for the phase(s) of the study in which they are enrolled. A subject will be discontinued from the study for any of the following reasons:

- Pregnancy
- At the discretion of the investigator at any time
- At the subject's request
- Occurrence of a treatment-emergent adverse event (TEAE) or considerable worsening of an AE that, in the opinion of the investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the subject if he/she continues in the study. The investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- Lack of tolerability to <<drug or device>>
- Failure to continue to meet inclusion/exclusion criteria

Any enrolled subjects desiring to discontinue prior to study completion should be encouraged to discuss his or her reasons and concerns with the investigator. If, after discussion, the subject still chooses to discontinue participation in the study, the subject should be encouraged to attend a <<final safety evaluation or follow-up visit or study visit>>. Subject participation in the study is purely voluntary. Subjects who are discontinued outside of any scheduled visit will be encouraged to complete the <<early termination visit or final study visit>> at the time of discontinuation. Subjects who are discontinued during a scheduled visit will be encouraged to complete all unique assessments for both that study visit and the <<early termination visit or final study visit>> at the time of discontinuation. A subject who discontinues following <<the injection, study drug administration, x>> will not be replaced. (Note that an early termination visit is not always applicable, and the default is the final study visit; if an early termination visit will be included, a separate description regarding the parameters for early termination will be necessary)

5.5. Stopping Rules

This study may be discontinued at any time if, in the opinion of the Investigator or the Sponsor, continuation of the study represents a significant medical risk to participating subjects. (Example text is included – Add to and/or update with information applicable to the study; specific stopping rules should be listed here. Describe role, if any, for a DSMB in safety data review and role in recommending study stopping.)

6. STUDY SCHEDULE AND PROCEDURES

6.1. Study Schedule

The study schedule can be found in Table 3~~Table 3~~. Detailed information on study assessments is provided in Section 7.

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6.2. Study Visits

<<Describe details of each treatment visit (e.g., Screening, Baseline, various Treatment Visits, Follow Up, etc.), including visit timing (by year, month, week, day, or hour, as appropriate, based on "Day 1" as time of first administration of treatment), the permitted window for the visit (for example, +/- 1 week), and bulleted list of procedures. If appropriate to the study, visits may be grouped by study phase and this section organized by these groupings. If applicable, remember to describe the components of an Early Termination Visit and how unscheduled visits will be handled; Note: For logistical reasons as well as compliance with FDA-approved standards such as SDTM, the Study Schedule should NOT include a Day 0/Visit 0 time point.>>

Subjects may experience AEs that necessitate an unscheduled visit. There may also be situations in which the investigator asks a subject to report for an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of subjects during the study. <<Case report forms (CRFs) or Electronic case report forms (eCRFs)>> should be completed for each unscheduled visit. (Example text– Add to and/or edit as applicable to the study)

6.2.1. Screening Visit / Visit 1 (Week -4 to -1)

<<Include a bulleted list of procedures, including time points and volume of draws for PK assessments, if applicable to the study; detailed assessments are found in Section 7.>>

6.2.2. Baseline Visit / Visit 2 (Week 1)

<<Include additional subsections for each protocol visit.>>

<<Table 3 may be best presented as an appendix, as a landscape format, and/or on a separate page). Further, depending on the length of Table 3, it may or may not fit onto a single page. In such cases, use the StartingPoint toolbar function to break the table across pages to preserve table title and column headings.>>

Table 3: Study Schedule

	Study Phase							
	Screening	Baseline	Treatment			Follow-up		
Visit	X	X	X	X	X	X	X	X
Days	X	X	X	X	X	X	X	X
Window (Days)			X	X	X	X	X	X
Informed Consent	X							
Eligibility Assessments	X	X						
X-ray	X							
Vital Signs	X							
BMI (Height, Weight)	X							
Medical History	X	X						
Prohibited Medications/Therapies	X	X						
Pregnancy Test	X							
Laboratory Tests	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Additional Assessment 1		X	X	X	X	X	X	X
Additional Assessment 2	X	X	X	X	X	X	X	X
Additional Assessment 3		X	X	X	X			
Additional Assessment 4	X	X	X	X	X	X	X	X
Additional Assessment 5	X	X	X	X	X	X	X	X
Additional Assessment 6	X	X	X	X	X	X	X	X

Additional Assessment 7	X	X	X	X	X	X	X	X
Additional Assessment 8	X	X	X	X	X			
Additional Assessment 9		X	X	X	X			
Additional Assessment 10		X	X	X	X			
Additional Assessment 11	X	X	X	X	X	X	X	X
End of Study Form								X

(Sample Table of Study Schedule – Add to and/or update with information applicable to the study)
Note: The Study Schedule should NOT include a Day 0/Visit 0 time point.

7. ASSESSMENTS

7.1. <<Efficacy or Effectiveness>> Assessments

<<Include the specification(s) of efficacy/effectiveness parameter(s) for the study, relative to measurable outcomes identified in the study objectives and/or endpoints within Sections 3 and 4, respectively; studies with multiple efficacy/effectiveness assessments may include each assessment as a subheading (e.g. 14.1. Patient Evaluation), with a paragraph description of the details and/or procedures for that assessment; Refer to the Study Schedule and Procedures (Section 6) for specific information on visit activities; copies of specific assessment tools may be referenced and included in the Appendix (Section 19) as applicable. Keep in mind that specifying the study visit for each assessment is a risk and will require additional QC time. Also, if a change is made in the schedule of events during protocol development/reiveiw and/or in an amendment to the protocol, this will create more work and QC time>> (Example assessments are below - Add to and/or update with information applicable to the study. For assessments requiring trained/experienced rater, consider including a statement to that effect [Training on the <<X Scale>> will be required for those who have not received training in the 12 months prior to performing this study assessment. Designated, qualified individuals from the study research team will perform the assessment.] Also, consider including a statement to encourage that the same rater be maintained for the assessment [The site will make all efforts to maintain the same rater across other visits for each individual subject.])

7.1.1. Primary <<Efficacy/Effectiveness>> Assessment

7.1.2. Secondary <<Efficacy/Effectiveness>> Assessment

7.2. Safety Assessments

<<Include the specification(s) of safety parameter(s) for the study; studies with multiple assessments may include each assessment as a subheading, with a paragraph description of the details and/or procedures for that assessment; sample assessments may be referenced and included in the Appendix (Section 19) as applicable>> (Example assessments and text are below - Add to and/or update with information applicable to the study)

All subjects who enter the study will be assessed for safety. Safety will be monitored by observation of and direct inquiry regarding AEs at each post-dose visit.

7.2.1. Adverse Events

All AEs will be collected from the start of <<informed consent or administration of investigational product>> through the Study Visit X after the last administration of study <<drug/device/product>>. Details regarding AE definitions, collection, recording, and reporting are found in Section 11.1 .

7.2.2. Demographic/Medical History

Information relating to the subject's sex, age, race, height, and weight will be recorded at Screening on the appropriate <<eCRF or CRF>> page. Medical history of each subject will be collected at <<Screening, Baseline, and/or Study Visits X>> and recorded on the appropriate <<eCRF or CRF>> page.

7.2.3. Physical Examination

A <<complete or abbreviated>> physical examination will be performed at <<Screening, Baseline, and/or Study Visits X>>. This will include physical examination of the following body areas and systems: <<head and neck, abdominal, chest, cardiovascular, heart, respiratory, musculoskeletal, skin, neurological, and/or endocrine>>. This assessment is <<optional or mandatory>> at unscheduled visits and the early termination visit, per the Investigator's discretion.

Body weight will also be measured at <<Screening, Baseline, and/or Study Visits X>>. Height will be measured at <<Screening, Baseline, and/or Study Visits X>>.

7.2.4. Vital Signs

Blood pressure and pulse will be assessed at <<all visits, Screening, Baseline, and/or Study Visits X>> and will be taken using <<e.g., automated machines programmed to take 3 consecutive readings (at least 2 minutes apart)>>. Subjects should be comfortably seated for << X minutes>> prior to blood pressure readings. Study staff will take care to select the appropriate cuff size for each subject. Respiratory rate and temperature will be measured at <<all visits, Screening, Baseline, and/or Study Visits X>>.

7.2.5. Concomitant Medications/Therapies

All concomitant medications/therapies collected throughout the study must be recorded on the Concomitant Medication <<eCRF or CRF>>. The <<prohibited and/or allowed>> concomitant medications/therapies for the study are discussed in Section X.

7.2.6. Electrocardiography (ECG)

A 12-lead ECG will be recorded and assessed at <<all visits, Screening, Baseline, and/or Study Visits X>> by the Investigator or other designated, qualified individual from the study research team at a <<central ECG facility or insert specific ECG facility>>. This assessment is <<optional or mandatory>> at unscheduled visits and an early termination visit, per the Investigator's discretion.

7.2.7. Laboratory Assessments

7.2.7.1. Hematology, Serum Chemistry, and Urinalysis

At <<all visits, Screening, Baseline, and/or Study Visits X>>, laboratory tests will include <<a non-fasting serum chemistry panel, hematology (CBC), and/or urinalysis>> for <<X assessments, e.g., prohibited concomitant medications, etc.>> (Appendix). For a complete list of laboratory tests, refer to Appendix X. (For extensive hematology, serum chemistry, and urinalysis assessments, these assessments can each be described within separate subheading sections).

7.2.7.2. Virus Serology

Subject sera will be screened for the presence of <<antibodies and/or antigens>> for <<HIV, Hepatitis B virus, and/or Hepatitis C virus infections, etc.>> at <<all visits, Screening, Baseline, and/or Study Visits X>>.

7.2.7.3. Pregnancy Screen

At <<all visits, Screening, Baseline, and/or Study Visits X>>, a <<serum and/or urine dipstick>> pregnancy test will be performed for << all female subjects or female subjects of child-bearing potential>>.

Additionally, a <<serum and/or urine dipstick>> pregnancy test may be performed at any time during study participation if pregnancy is suspected.

7.2.7.4. Drug, Alcohol, and Nicotine Screen

Urine for a drug, alcohol, and nicotine screening will be collected from subjects as part of the Clinical Laboratory Testing at <<screening>>. Samples should be tested for the presence of <<alcohol, nicotine, cocaine, marijuana, opiates, benzodiazepines, amphetamines, and/or barbiturates>>. Subjects with positive screen test results for any of the above substances will be excluded from this study with the exception of a positive result from <<their current ADHD therapy>>. Positive drug, alcohol, and nicotine tests cannot be repeated.

7.3. Pharmacokinetic Assessments

<<Include the specification(s) of pharmacokinetic parameter(s) for the study; studies with multiple assessments may include each assessment as a subheading, with a paragraph description of the details and/or procedures for that assessment>> (Example assessments and text are below - Add to and/or update with information applicable to the study)

Pharmacokinetic (PK) <<blood and/or other bodily fluid>> samples, at <<X time points, e.g., trough (pre-administration) and at the time of maximum plasma concentration (T_{max}), X minutes/hours post-administration>>, will be collected from each subject by a designated, qualified individual from the study research team at <<all visits, Screening, Baseline, and/or Study Visits X>>. Instructions for processing, storage, and shipping of PK samples will be provided to each site. Pharmacokinetic samples will be analyzed by <<laboratory processing/bioanalytical site>>.

8. INVESTIGATIONAL <<DRUG OR DEVICE>> INFORMATION AND MANAGEMENT

8.1. Investigational <<Drug or Device>> Dose Regimen

<<An adequately detailed description of the investigational product, including the name(s) of the product(s), the dose(s)/type(s), the treatment schedule(s), the route(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial>>

8.2. Dose Rationale

<<Provide sufficient background and summary information to explain why dose level(s) were chosen for the study. If this is an escalating-dose study, include criteria for increasing doses. Cross-reference section describing role of data oversight board (e.g., DSMB) in facilitating dose-escalation decisions, if applicable.>>

8.3. Investigational <<Drug or Device>> Packaging and Labeling

All investigational <<drugs or devices>> used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures (SOPs) of Rho or those of its designee, Good Manufacturing Practice (GMP) guidelines, International Conference on Harmonization (ICH) guidelines for GCP, guidelines for Quality System Regulations (QSR), and applicable regulations.

<<1-2 paragraph description of investigational product manufacturing, including entities involved in packaging and labeling>>

8.4. Investigational <<Drug or Device>> Storage

<<1-2 paragraph description of investigational product storage procedures, such as post-delivery handling and storage, in accordance with ICH GCP, GMP, and/or QSR guidelines; if the product is a controlled substance (e.g., Schedule II), consider including a statement such as <<Drug>> is a Schedule II controlled substance and must be handled and stored in accordance with federal and local guidelines.>>

8.5. Investigational <<Drug or Device>> Preparation

<<1-2 paragraph description of the procedure(s) needed for investigational product preparation; likely more applicable to drugs than devices because drugs may need resuspension, mixing, etc.>> (This section this section may be omitted if not applicable)

8.6. Investigational <<Drug or Device>> Administration

<<A clear and complete description of the investigational product administration procedures, which may be provided in a numbered or bulleted list; additional details may include procedure variations with respect to treatment visits, subject populations, blinding/randomization, and any warnings associated with administration of the product>>

8.7. Investigational <<Drug or Device>> Accountability

<<1-2 paragraph description of investigational product accountability procedures, such as post-treatment handling and disposal, in accordance with ICH GCP/GMP/QSR guidelines; guidelines regarding accountability record keeping may also be included via a bulleted list>>

8.8. Investigational <<Drug or Device>> Handling and Disposal

<<1-2 paragraph description of investigational product post-treatment handling and disposal, in accordance with ICH GCP/GMP/QSR guidelines>> (Note: this section may be grouped with the Accountability section if the description of accountability, handling, and disposal of the investigational product is not too lengthy or complex)

9. TREATMENT OF SUBJECTS

9.1. Rescue Medication

<<Approximately 1 paragraph description of rescue medication(s) permitted during the trial and the procedures for administration, if applicable>> (This section this section may be omitted if not applicable)

9.2. Concomitant <<Medication and/or Treatment>>

<<Approximately 1-2 paragraph description of medication(s)/treatment(s) permitted or not permitted before and/or during the trial, and the procedures for administration, if applicable>>

9.3. Other Study Restrictions

<If applicable, describe any restricted activities, foods, or other therapies such as chiropractic or massage therapy, and the timing of these restrictions with respect to specific protocol activities, in detail if extensive restrictions are required for the study.>>

9.4. Treatment Compliance

<<Approximately 1-2 paragraph description of procedures for monitoring subject compliance (e.g., subject diaries, interim blood draws, etc.); subheadings for assessments for treatment compliance may be included in separate subheadings.>>

10. RANDOMIZATION AND BLINDING PROCEDURES

<<Approximately 1-3 paragraph description of randomization (e.g., web-based central randomization system) and blinding procedures for the trial (e.g., subject assignments, blinding of site personnel, and circumstances which blinding may be broken [e.g., medical emergency]); Also, include a description of the number of subjects planned to be enrolled and randomized into the respective treatment arms of the study (in multicenter trials, the number of enrolled subjects projected for each trial site should be specified). Also describe stratification plans for randomization, but do not disclose the blocking strategy for randomization, as this may partially unblind the site staff.>>

11. ADVERSE EVENTS

TO THE AUTHOR: Use Section 11.1 if the investigational product is a drug/biologic; use Section 11.2 if the investigational product is a device. Be sure to completely delete the section that is not used in the protocol and update the TOC.

11.1. Adverse and Serious Adverse Events

<<Approximately 1 paragraph description on how/when AEs will be assessed over the course of the study (e.g., at Screening, Baseline, Treatment, and Follow-up visits)>> (Sample text for drugs/biologics is below – Add to and/or update with information applicable to the study)

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21 Code of Federal Regulations (CFR) 312, ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and ICH Guideline E-6: Guidelines for Good Clinical Practice.

Adverse events will be recorded throughout the study and at early termination, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the investigational product. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE <<or AE of interest>> requiring immediate notification to the Sponsor or its designated representative.

11.1.1. Definitions of Adverse Events

11.1.1.1. Adverse Event (AE)

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (ICH E6 Guidelines for GCP). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

11.1.1.2. Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor whether it is considered treatment related or not.
- A life-threatening event: An AE or suspected adverse reaction (SAR) is considered "life-threatening" if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of investigational product dependency or abuse.
- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study product, the event must be reported to the Sponsor as described in Section 11.1.5.

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. Any hospitalization except observational admissions of less than 24 hours meets these criteria. This category also includes transfer within the hospital to an acute/intensive care unit (e.g., from a standard of care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g. caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g. for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject.
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

11.1.1.3. Adverse Drug Reaction (ADR) and Suspected Adverse Reaction (SAR)

An adverse drug reaction (ADR) means any AE caused by a <<drug or biologic>>.

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the <<drug or biologic>> caused the AE. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the <<drug or biologic>> and the AE. An SAR implies a lesser degree of certainty about causality than an ADR (21 CFR 312.32(a)).

11.1.1.4. Unexpected Adverse Reaction (UAR)

The Sponsor is responsible for assessing AEs for expectedness. With regards to reporting to the Health Authority, an AE is considered "unexpected" when its nature (specificity), severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the protocol/package insert/investigator's brochure/prescribing information for <<study drug(s)>>. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the investigator's brochure as occurring with a class of <<drugs or biologics>> or as anticipated from the pharmacological properties of the <<drug or biologic>> but are not specifically mentioned as occurring with the particular <<drug or biologic>> under investigation (21 CFR 312.32(a)).

For a comparator product with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the <<Prescribing Information/Summary of Product Characteristics (SmPC)>>.

11.1.1.5. Adverse Events of Interest (AEIs)

This class of <<drugs or biologics>> has been reported to be associated with <<expected AEs, e.g. impaired liver/kidney function/AEs related to the gastrointestinal tract/skin, etc.>> For this trial, the AEs listed in Table X will be collected as AEs of interest (AEIs) and will be followed to outcome. The site will report any AEI within 48 hours of learning of the event. (Example text – Add to and/or update with information applicable to the study)

11.1.2. Severity of AEs/SAEs

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version 4.03*. This document (referred to herein as the "NCI-CTCAE manual") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of AEs. Please refer to the NCI-CTCAE manual for the desired event and specific grading for that event. (Note: this grading scale is the most commonly used in our trials; however, there may be a more appropriate scale depending on the indication)

If the event is not listed in the NCI-CTCAE manual, please refer to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = moderate minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 = life-threatening consequences; urgent intervention indicated.
- Grade 5 = death related to AE.

For additional information and a printable version of the NCI-CTCAE manual, go to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

The study site will grade the clinical severity of AEs experienced by study participants as either:

- Mild: Causes no limitation of usual activities
- Moderate: Causes some limitation of usual activities
- Severe: Prevents or severely limits usual activities

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 11.1.1.2 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on patient/adverse outcome. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

11.1.3. Relationship to Investigational <<Drug or Biologic>> Treatment

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE and must be provided for all AEs (serious and non-serious).

The Sponsor's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table X

Table X. Attribution of adverse events

Unrelated	The AE is clearly/most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention or concomitant therapy, or the delay between administration and the onset of the AE is incompatible with a causal relation, or the AE started before administration (screening phase). Therefore, there is not a reasonable possibility that the AE was caused by the investigational drug.
Related	There is a reasonable possibility that the AE was caused by the investigational drug. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (21 CFR 312.32(a)).

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. Any AE that is suspected to be related to the investigational product will be classified as an ADR.

11.1.4. Collecting and Recording Adverse Events

<<Brief, 1-2 paragraph description of the methods and timing for assessing, recording, and analyzing safety parameters for the trial>>

(Sample text below - Add to and/or update with information applicable to the study)

11.1.4.1. Period of Collection

All AEs will be collected from the time of <<e.g. informed consent/first treatment administration>> through <<e.g. the final study visit/30 days after the last dose>>. <<Can include if there are differences in what will be collected when (e.g. if only SAEs are collected from informed consent until first treatment or if grade 2 or higher only during the 30-day follow-up period>>. All AEs and SAEs should be treated as medically appropriate and followed until event resolution.

11.1.4.2. Methods of Collection

Adverse events may be collected as follows:

- Observing the participant
- Questioning the participant in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the participant

An abnormal value or result from a clinical or laboratory evaluation <<relevant assessments, e.g. a radiograph, an ultrasound, or ECG>> can also indicate an AE if it is determined by the investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

11.1.4.3. Recording Method

11.1.4.3.1. Adverse Events

All AEs occurring during this clinical study will be recorded by the Investigator on the appropriate <<CRF or eCRF>> in precise medical terms, along with the date <<and time>> of onset and the date <<and time>> of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should combine signs and symptoms into a single term that constitutes a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to <<study drug or biologic>>. The severity of the AE and its relationship to the <<study drug or biologic>> will be assessed by the Investigator.

The investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the concomitant medication <<CRF or eCRF>> as a concomitant medication administered. The action taken and the outcome must also be recorded. The investigator will follow a non-serious AE until resolution, stabilization of the Follow-up Visit. The investigator will follow an SAE (regardless of relationship to <<study drug or biologic>> until the event resolves, stabilizes, or becomes non-serious. The terms of AE resolution (i.e., recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, fatal, unknown) should also be recorded.

11.1.4.3.2. Serious Adverse Events

Serious adverse events will be recorded on the AE <<CRF or eCRF>> and on the SAE <<CRF or eCRF>>, and health authorities will be notified as outlined in Section 11.1.5.2.

11.1.5. Reporting Adverse Events

<<Brief (approximately 2-3 paragraph) description of procedures for eliciting reports of and for recording and reporting AE and intercurrent illnesses; include the type and duration of the follow-up of subjects after AEs>>

(Sample text below - Add to and/or update with information applicable to the study)

11.1.5.1. Reporting SAEs to the Sponsor

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the investigator or designee is responsible for reporting the SAE <<to Rho>>, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Reporter
- Subject ID
- Study product or intervention
- Serious AE term
- Relationship to study medication(s)
- Reason why the event is serious

Supplemental <<CRF or eCRF>> pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, study <<drug or biologic>> administration, and death as applicable.

Unavailable details of the event should not delay submission of the known information. As additional details become available, the SAE <<eCRF/report form>> should be updated and re-submitted <<via the EDC system and/or by fax>>.

For additional information regarding SAE reporting, contact:

11.1.5.2. Reporting Serious Adverse Events to Health Authorities

The Sponsor is responsible for reporting SAEs to the health authorities in accordance with the regulations for each country.

-OR-

The Sponsor will report Investigational New Drug (IND) Safety Reports to the FDA and investigators in accordance with the FDA regulations detailed in the 21 CFR 312.32. (US only)

-OR-

11.1.5.2.1. <<US or European Union>>

After the SAE has been reported by the site investigator and assessed by the IND sponsor, there are 2 options for the IND sponsor to report an event to the appropriate health authorities:

Standard reporting (report in the IND annual report) is required. This option applies if the AE is classified as one of the following

- Serious, SAR per the definitions section (Section 11.1.1)
- Serious and not an SAR per the definitions section (Section 11.1.1)

Expedited reporting is required. This option applies if the AE/safety finding is classified as one of the following

1. Serious and unexpected suspected adverse reaction (SUSAR) per the definitions section (Section 11.1.1)

   The Sponsor must report any SAR that is both serious and unexpected. The Sponsor must report AE as an SAR only if there is evidence to suggest a causal relationship between the study product and the AE, such as:

   - A single occurrence of an event that is uncommon and known to be strongly associated with the product treatment (e.g. <<relevant associated events, e.g. angioedema, hepatic injury, or Stevens-Johnson Syndrome>>);
   - One or more occurrences of an event that is not commonly associated with product treatment but is otherwise uncommon in the population exposed to the product (e.g. <<relevant associated events, e.g. tendon rupture>>);
   - An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of investigational product therapy) that indicates those events occur more frequently in the treatment group than in a concurrent or historical control group.
2. Any safety findings from other studies: The Sponsor must report any findings from other epidemiological studies, pooled analysis of multiple studies, or clinical or nonclinical studies that suggest a significant risk in humans exposed to the investigational product that would result in a safety-related change in the protocol, informed consent, investigator's brochure, or other aspects of the overall conduct of the study.

These events, which require unblinding, must be reported by the Sponsor to the appropriate health authorities within 15 calendar days; fatal or life-threatening events must be reported within 7 calendar days.

11.1.5.2.2. Mexico

All SAEs that occur in Mexico, regardless of expectedness or relationship to study product, must be reported to the Mexican Health Authority (using the Federal Commission for the Protection against Sanitary Risk [COFEPRIS) form] within 7 calendar days, and a follow-up report must be submitted within 15 calendar days.

11.1.5.2.3. Canada

After the SAE has been reported by the site investigator and assessed by the IND sponsor, there are two options for the IND sponsor to report an event to the health authorities in Canada:

Expedited reporting is required.

This option applies if the AE is classified as the following:

- Serious and unexpected suspected adverse reaction (SUSAR). The Sponsor must report any SAR that is both serious and unexpected.

The Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the AE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure (e.g. angioedema, hepatic injury, or Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with investigational product exposure, but is otherwise uncommon in the population exposed to the investigational product (e.g. tendon rupture)

These events, which are not required to be unblended at this time, must be reported by the Sponsor to the appropriate health authorities within 15 calendar days; fatal or life-threatening events must be reported within 7 calendar days. The Sponsor is responsible for disseminating reports to the health authorities and all investigators in the study.

Final study report

A complete summary of safety information is included in the final study report submitted at the closure of the protocol. This option applies if the AE is classified as one of the following:

- Serious, SAR
- Serious and not an SAR

11.1.5.3. Reporting Serious Adverse Events to <<Instiutional Review Boards or Ethics Committee(s)>>

It is the responsibility of the investigators to promptly notify their respective <<IRB(s) or Ethics Committee(s)>> of IND Safety reports or other matters involving risk to patients as mandated by the <<IRBs/ECs>>.

11.1.5.4. Reporting Serious Adverse Events to the Data Safety Monitoring Board

The Sponsor will provide the DSMB with data of all SAEs on an ongoing basis. (Remove if no DSMB for the study or change to SRC, ISM, etc. as needed)

11.1.5.5. Reporting Pregnancy

<<A brief (1-3 paragraphs) description of the procedures and timing for reporting suspected or confirmed pregnancies, including any impacts on trial participation>> (Example text below – Add to and/or edit with information applicable to the study)

During the study, all subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The investigator is responsible for reporting all available pregnancy information on the pregnancy <<CRF or eCRF>> within 24 hours of becoming aware of the event, although pregnancy itself if not considered an AE. <<The investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. –OR- Study treatment must be discontinued immediately in the event of a pregnancy. The patient should be referred to an

obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling>>. Monitoring of the participant should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available.

<<Partner pregnancies of a male subject do not need to be reported. –OR- Partner pregnancies of a male subject will be reported and followed to outcome (as described above/describe any differences in the process here)>>.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 11.1.5. Should the pregnancy result in a congenital abnormality or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the investigator suspects is related to the in-utero exposure to the study treatment should also be reported.

11.2. Adverse and Serious Adverse Events

<<Approximately 1 paragraph description on how/when AEs will be assessed over the course of the study (e.g. at Screening, Baseline, Treatment, and Follow-up visits)>> (Sample text for device products is below – Add to and/or update with information applicable to the study)

This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21 Code of Federal Regulations (CFR) 312, ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and ICH Guideline E-6: Guidelines for Good Clinical Practice.

Adverse events will be recorded throughout the study and at early termination, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The investigator is responsible for the detection and documentation of AEs regardless of treatment group or suspected causal relationship to the investigational device. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE <<or AE of interest>> requiring immediate notification to the Sponsor or its designated representative.

11.2.1. Definitions of Adverse Effects

11.2.1.1. Adverse Event (AE)

An AE is defined as any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (ICH E6 Guidelines for GCP). Any medical condition that is present at the time that the subject is screened will be considered as medical history and not recorded as an AE; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

11.2.1.2. Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes (21 CFR 312.32(a)):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor whether it is considered treatment related or not.
- A life-threatening event: An AE or adverse device effect (ADE) is considered "life-threatening" if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE or ADE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.
- Congenital anomaly or birth defect.

If an event meets any of the above definitions, regardless of the severity or relationship of the event to the study device, the event must be reported to the Sponsor as described in Section 11.1.5.

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a hospital meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g. from the medical floor to the intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g. caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Protocol-specified admission (e.g. for a procedure required by the study protocol)
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject.

- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

11.2.1.3. Adverse Device Effect (ADE)

An adverse device effect (ADE) is an AE that is suspected to be related to the device. Adverse device effects can be either anticipated, which means that they have been previously identified in this protocol or the investigator's brochure, or unanticipated.

11.2.1.4. Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is a serious ADE that is unanticipated, occurs at a frequency higher than anticipated, or is of a nature, severity, specificity, or outcome that is not anticipated.

11.2.1.5. Adverse Events of Interest (AEIs)

This class of devices has been reported to be associated with <<expected AEs, e.g. impaired liver/kidney function/AEs related to the gastrointestinal tract/skin, etc.>> For this trial, the AEs listed in Table X will be collected as AEs of interest (AEIs) and will be followed to outcome. The site will report any AEI within 48 hours of learning of the event. (Example text – Add to and/or update with information applicable to the study)

11.2.2. Severity of AEs/SAEs

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version 4.03*. This document (referred to herein as the "NCI-CTCAE manual") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of AEs. Please refer to the NCI-CTCAE manual for the desired event and specific grading for that event. (Note: this grading scale is the most commonly used in our trials; however, there may be a more appropriate scale depending on the indication)

If the event is not listed in the NCI-CTCAE manual, please refer to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = moderate minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 = life-threatening consequences; urgent intervention indicated.
- Grade 5 = death related to AE.

For additional information and a printable version of the NCI-CTCAE manual, go to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

The study site will grade the clinical severity of AEs experienced by study participants as either:

- Mild: Causes no limitation of usual activities
- Moderate: Causes some limitation of usual activities
- Severe: Prevents or severely limits usual activities

Note: The terms serious and severe are not synonymous. Serious criteria as defined in Section 11.1.1.2 above serve as a guide for defining regulatory reporting obligations. The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache); the event itself, however, may be of relatively minor medical significance. This is not the same as serious, which is based on patient/adverse outcome. Therefore, an AE of severe headache might not be considered serious, but a moderate infection for which a subject is hospitalized should be reported as an SAE.

11.2.3. Relationship to Investigational Device Treatment

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational device caused or contributed to an AE and must be provided for all AEs (serious and non-serious).

The Sponsor's determination of attribution will be used for reporting to the appropriate health authorities. The relation of an AE to study participation will be determined using the descriptors and definitions provided in Table X (Choose appropriate causality option/Sponsor preference below).

Table X. Attribution of adverse events

Unrelated	The AE is clearly/most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention or concomitant therapy, or the delay between administration and the onset of the AE is incompatible with a causal relation, or the AE started before administration (screening phase). Therefore, there is not a reasonable possibility that the AE was caused by the investigational device.
Related	There is a reasonable possibility that the AE was caused by the investigational device. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship (21 CFR 312.32(a)).

-OR-

Table X. Attribution of adverse events

Unrelated	The AE is clearly not related.
Possible	The AE has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
Definite	The AE is clearly related.

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. Any AE that is suspected to be related to the investigational device will be classified as an ADE.

11.2.4. Collecting and Recording Adverse Events

<<Brief, 1-2 paragraph description of the methods and timing for assessing, recording, and analyzing safety parameters for the trial>>

(Sample text below - Add to and/or update with information applicable to the study)

11.2.4.1. Period of Collection

All AEs will be collected from the time of <<e.g. informed consent/first treatment administration>> through <<e.g. the final study visit/30 days after the last treatment>>. <<Can include if there are differences in what will be collected when (e.g. if only SAEs are collected from informed consent until first treatment or if grade 2 or higher only during the 30-day follow-up period)>>. All AEs and SAEs should be treated as medically appropriate and followed until event resolution.

11.2.4.2. Methods of Collection

Adverse events may be collected as follows:

- Observing the participant
- Questioning the participant in an unbiased and non-leading manner
- Receiving an unsolicited complaint from the participant

An abnormal value or result from a clinical or laboratory evaluation <<relevant assessments, e.g. a radiograph, an ultrasound, or an electrocardiogram>> can also indicate an AE if it is determined by the investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stable establishing a new baseline and the participant's safety is not at risk.

11.2.4.3. Recording Method

11.2.4.3.1. Adverse Events

All AEs occurring during this clinical study will be recorded by the Investigator on the appropriate <<CRF or eCRF>> in precise medical terms, along with the date <<and time>> of onset and the date <<and time>> of resolution. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should combine signs and symptoms into a single term that constitute a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness, and relatedness to the study <<device>>. The severity of the AE and its relationship to the study <<device>> will be assessed by the Investigator.

The Investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes. If any medication is administered in response to the AE, this medication should be noted on the concomitant medication <<CRF or eCRF>> as a concomitant medication administered. The action taken and the outcome must also be recorded. The

investigator will follow a non-serious AE until resolution, stabilization of the Follow-up Visit. The investigator will follow an SAE (regardless of relationship to <<study drug or biologic>> until the event resolves, stabilizes, or becomes non-serious. The terms of AE resolution (i.e., recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, fatal, unknown) should also be recorded.

11.2.4.3.2. Serious Adverse Events

Serious adverse events will be recorded on the AE <<CRF or eCRF>> and on the SAE <<CRF or eCRF>>, and health authorities will be notified as outlined in Section 11.1.5.2.

11.2.5. Reporting Adverse Events

<<Brief (approximately 2-3 paragraph) description of procedures for eliciting reports of and for recording and reporting AE and intercurrent illnesses; include the type and duration of the follow-up of subjects after AEs>>

(Sample text below - Add to and/or update with information applicable to the study)

11.2.5.1. Reporting SAEs/UADEs to the Sponsor

The following process for reporting an SAE ensures compliance with 21 CFR 312 and ICH guidelines. After learning that a participant has experienced an SAE, the investigator or designee is responsible for reporting the SAE <<to Rho>>, regardless of relationship or expectedness, within 24 hours of becoming aware of the event. The initial SAE report should include as much information as possible, but at a minimum must include the following:

- Name of the Reporter
- Subject identification
- Study <<device/intervention>>
- Serious AE term
- Date of onset
- Relationship to study <<device/intervention>>
- Reason why the event is serious

Supplemental <<CRF or eCRF>> pages should be current at the time of SAE reporting: medical history, concomitant medications, demographics, study device administration, and death as applicable.

Unavailable details of the event should not delay submission of the known information. As additional details become available, the SAE <<eCRF/report form>> should be updated and re-submitted <<via the EDC system and/or by fax>>.

Any UADE must be reported by the investigator to the <<Sponsor and/or Rho>> and the reviewing Institutional Review Board (IRB) as soon as possible but no later than 10 working days after the investigator first learns of the effect. <<The Sponsor and/or Rho>> shall immediately conduct an evaluation of any reported SAE to determine whether it meets UADE reportable criteria. If the <<Sponsor and/or Rho>> determine that a UADE presents an unreasonable risk to subjects, <<the Sponsor and/or Rho>> shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur no later than 5 working days after the <<Sponsor and/or Rho>>

make this determination and no later than 15 working days after <<the Sponsor and/or Rho>> first receives notice of the effect.

<<The Sponsor and/or Rho>> will report the results of any investigation of a UADE to the FDA and to all reviewing IRBs and participating investigators within 10 working days.

For additional information regarding SAE/UADE reporting, contact Rho Product Safety:

Rho Product Safety
6330 Quadrangle Drive, Suite 500
Chapel Hill, NC 27517
Toll-free: 1-888-746-7231
SAE Fax Line: 1-888-746-3293
Email: rho_productsafety@rhoworld.com

11.2.5.2. Reporting SAEs to Health Authorities

Comment [LN3]: Authors: The text in this section was drafted for drug products/biologics. The text may need to be modified for devices.

The Sponsor is responsible for reporting SAEs to the health authorities in accordance with the regulations for each country.

-OR-

The Sponsor will report <<Investigational New Drug (IND) and/or Investigational Device Exemption (IDE)>> Safety Reports to the FDA and investigators in accordance with the FDA regulations detailed in the Code of Federal Regulations (CFR) 21 CFR 312.32. (US only)

-OR-

11.2.5.2.1. <<US or European Union>>

After the SAE has been reported by the site investigator and assessed by the IND sponsor, there are two options for the IND sponsor to report an event to the appropriate health authorities:

Standard reporting (report in the IND annual report) is required. This option applies if the AE is classified as one of the following

- Serious, SAR per the definitions section (Section 11.1.1)
- Serious and not an SAR per the definitions section (Section 11.1.1)

Expedited reporting is required. This option applies if the AE is classified as one of the following

3. Serious and unexpected suspected adverse reaction (SUSAR) per the definitions section (Section 11.1.1)

The Sponsor must report any SAR that is both serious and unexpected. The Sponsor must report AE as an SAR only if there is evidence to suggest a causal relationship between the study product and the AE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with the product treatment (e.g. <<relevant associated events, e.g. angioedema, hepatic injury, or Stevens-Johnson Syndrome>>);
- One or more occurrences of an event that is not commonly associated with product treatment but is otherwise uncommon in the population exposed to the product (e.g. <<relevant associated events, e.g. tendon rupture>>);

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of investigational product therapy) that indicates those events occur more frequently in the treatment group than in a concurrent or historical control group.

4. Any findings from other studies: The Sponsor must report any findings from other epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the device that would result in a safety-related change in the protocol, informed consent, investigator's brochure, or other aspects of the overall conduct of the study.

These events, which require unblinding, must be reported by the Sponsor to the appropriate health authorities within 15 calendar days; fatal or life-threatening events must be reported within 7 calendar days.

11.2.5.2.2. Mexico

All SAEs that occur in Mexico, regardless of expectedness or relationship to the study device, must be reported to the Mexican Health Authority (using the Federal Commission for the Protection against Sanitary Risk [COFEPRIS) form] within 7 calendar days, and a follow-up report must be submitted within 15 calendar days.

11.2.5.2.3. Canada

After the SAE has been reported by the site investigator and assessed by the IND sponsor, there are two options for the IND sponsor to report an event to the health authorities in Canada:

Expedited reporting is required.

This option applies if the AE is classified as the following:

- Serious and unexpected suspected adverse reaction (SUSAR). The Sponsor must report any SAR that is both serious and unexpected.

The Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the investigational device and the AE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with the device exposure (e.g. angioedema or hepatic injury)
- One or more occurrences of an event that is not commonly associated with device exposure but is otherwise uncommon in the population exposed to the device (e.g. tendon rupture)

These events, which are not required to be unblended at this time, must be reported by the Sponsor to the appropriate health authorities within 15 calendar days; fatal or life-threatening events must be reported within 7 calendar days. The Sponsor is responsible for disseminating reports to the health authorities and all investigators in the study.

Final study report

A complete summary of safety information is included in the final study report submitted at the closure of the protocol. This option applies if the AE is classified as one of the following:

- Serious, SAR

- Serious and not an SAR

11.2.5.3. Reporting SAEs to <<IRB(s) or Ethics Committee(s)>>

It is the responsibility of the investigators to promptly notify their respective <<IRB(s) or Ethics Committee(s)>> of IND Safety reports or other matters involving risk to patients as mandated by the <<IRBs/ECs>>.

11.2.5.4. Reporting SAEs to the DSMB

The Sponsor will provide the DSMB with data of all SAEs on an ongoing basis. (Remove if no DSMB for the study or change to SRC, ISM, etc. as needed)

11.2.5.5. Reporting Pregnancy

<<A brief (1-3 paragraphs) description of the procedures and timing for reporting suspected or confirmed pregnancies, including any impacts on trial participation>> (Example text below – Add to and/or edit with information applicable to the study)

During the study, all subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The investigator is responsible for reporting all available pregnancy information within 24 hours of becoming aware of the event. <<The investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. –OR- Study treatment must be discontinued immediately in the event of a pregnancy. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling>>. Monitoring of the participant should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy should be reported as it becomes available.

<<Partner pregnancies of a male subject do not need to be reported. –OR- Partner pregnancies of a male subject will be reported and followed to outcome (as described above/describe any differences in the process here)>>.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 11.1.5. Should the pregnancy result in a congenital abnormality or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the investigator suspects is related to the in-utero exposure to the study treatment should also be reported.

12. STATISTICS

12.1. Power and Sample Size Determination

<<Brief (1-2 paragraphs) description of the sample size for the study and the statistical methods used to determine sample size for the study, including any relevant parameters, assumptions, and clinical justification (e.g. power, expected mean difference, standard deviation, etc.)>>.

12.2. Analysis Populations

<<Define the analysis populations for the study (e.g. safety population, intent-to-treat [ITT] population, and per-protocol [PP] population); also include how deviations from the original statistical plan will be reported and justified in the protocol and/or final report, as appropriate>> (Sample text is below – Add and/or modify with information applicable to the study)

The analysis populations are defined as follows:

- The safety population is defined as all randomized subjects who receive the study <<drug/device/intervention>>.
- The intent-to-treat (ITT) population is defined as all randomized subjects. <<add additional restrictive logic for a modified ITT (mITT)>>
- The per-protocol (PP) population is defined as all ITT subjects who have no major protocol deviations. The details of major protocol deviations will be defined in the statistical analysis plan. The PP population will be identified prior to unblinding/unmasking.

The <<efficacy or effectiveness>> analyses will be performed on the ITT population <<or mITT>>. <<Efficacy or Effectiveness>> analyses of the PP population will be supportive of the ITT analysis.

The safety analyses will be performed on the safety population.

12.3. <<Efficacy or Effectiveness>> and Safety Analyses

12.3.1. Background and Demographic Characteristics

<<Brief (2-4 sentences) description of how baseline demographic/background variables will be analyzed (e.g. by treatment group and overall) >>

12.3.2. <<Efficacy or Effectiveness>> Analyses

12.3.2.1. Primary <<Efficacy or Effectiveness>> Analys(is/es)

<<Brief (1-3 paragraph) description of how the primary efficacy/effectiveness analys(is/es) will be performed, including relevant outcome measures, treatment durations, etc. Provide a general description of the methodology/analyses to be employed. If using a longitudinal model for these analyses, state so here. Generally, the text here should provide sufficient detail to provide a statistical reviewer confidence in the general analysis strategy.>>

<<NOTE: FDA commonly requires for device trials a separate discussion of analyses to assess "study success criterion" with respect to "clinical significance". >>

12.3.2.2. Secondary <<Efficacy or Effectiveness>> Analys(is/es)

<<Brief (1-3 paragraph) description of how the secondary efficacy/effectiveness analys(is/es) will be performed, including relevant outcome measures, treatment durations, etc. Provide a general description of the methodology/analyses to be employed. If using a longitudinal model for these analyses, state so here. Generally, the text here should provide sufficient detail to provide a statistical reviewer confidence in the general analysis strategy.>>

12.3.3. Safety Analyses

12.3.3.1. Adverse Events

<<1-3 paragraph description of how AEs will be analyzed (e.g., by treatment group, severity, relationship to study procedure/treatment, etc.); consider duration of treatment phases, doses, etc. as applicable>>
(Sample text is below – Add to and/or modify with information applicable to the study)

Treatment-emergent AEs (any AEs recorded during or following the study injection) will be summarized by treatment group and categorized by severity and relationship to the study procedures and to the investigational <<drug or device>>. If a subject has more than 1 occurrence of the same AE, he/she will be counted only once within that preferred term in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study procedures and investigational <<drug or device>>, will be indicated in cases of multiple occurrences of the same AE. Serious adverse events and AEs of special interest also will be summarized separately. All AEs will be presented in a listing. Additionally, listings of SAEs and AEs leading to discontinuation will be generated. All SAEs will be evaluated to determine whether they are <<UARs or UADEs>>.

12.3.4. Concomitant Medications <<and Concomitant Therapies>>

<<Brief (1-2 sentence) description of how concomitant medications (and therapies, if applicable) will be analyzed and/or listed, as appropriate>>

12.3.5. Pharmacokinetic Analyses

<<Brief (1-2 sentence) description of how pharmacokinetic samples will be analyzed and/or listed (e.g., summarized in total and listed by-subject), as appropriate>>

12.4. Other Statistical Considerations

12.4.1. Significance Levels

<<1-2 sentence description of the significance level for each set of study analyses as applicable (e.g., type I error = 5% significance level). >>

12.4.2. Multiple Comparisons

<<Brief (1-2 paragraphs) description of multiple comparisons analyses, as applicable.>>

12.4.3. Missing Data

<<Detailed description of procedures for accounting for/analyzing missing, unused, and spurious data. A more-detailed discourse on the methods to be employed for missing data should be prepared for inclusion as an appendix.>>

12.4.4. Visit Windows

All data collected during study follow-up will be displayed and analyzed according to the actual visit data in the <<CRF or eCRF>>. Assessments taken outside of windows described in the protocol will be displayed according to the <<CRF or eCRF>> assessment recorded by the investigator.

12.5. Data Safety Monitoring Board Support

<<Describe timing and general level of details of displays to be prepared to support DSMB meetings>>

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

According to ICH GCP guidelines, the sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the <<CRFs or eCRFs>>. <<Rho or its designee and/or the Sponsor>> is/are responsible for assigning the study monitor(s) to this study. The study monitor's duties are to aid the investigator and Rho in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, <<IRB(s) or Ethics Committee(s)>> review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an investigational <<drug or device>> as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the <<CRFs or eCRFs>> and source documentation throughout the study to protect the rights of the subjects; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the clinical monitoring plan. (Sample text– Add to and/or modify with information applicable to the study)

13.2. Source Documents

<<Rho or its designee and/or the Sponsor>> requires that the investigator prepare and maintain adequate and accurate records for each subject treated with the investigational <<drug or device>>. Source documents such as any hospital, clinic, or office charts and the signed informed consent forms are to be included in the investigator's files with the subject's study records.

Study data will be captured <<by paper or electronically>>. Study site personnel will record <<CRF or eCRF>> data from source documents. Subjects will record selected study assessments directly into the <<CRF or eCRF>>. If any data are first recorded onto documents such as laboratory reports, these documents will be considered source. (Sample text– add to and/or modify with information applicable to the study)

13.3. Data Collection and Management

This study will be conducted in compliance with the ICH document "Guidance for Industry-E6 Good Clinical Practice: Consolidated Guidance," dated April 1996. This study will also be conducted in accordance with the Declaration of Helsinki (2013).

This study will use <<paper or electronic>> data collection (techniques to collect data directly from the investigational site using <<CRFs or eCRFs>>). The data will be stored centrally in a fully validated clinical database. The investigator is responsible for ensuring that all sections of each <<CRF or eCRF>> are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform 100% source document verification to ensure there are no inconsistencies between the <<CRFs or eCRFs>> and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the clinical monitoring plan. (Reference targeted source documentation plan, e.g., Clinical Monitoring Plan, as applicable).

At intervals throughout the study and upon completion, data will be exported from the database into SAS datasets.

Data management will be coordinated by the data managers of <<Sponsor, vendor, or Rho>> in accordance with their SOPs for data management and a formal study data management plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using World Health Organization – Drug Reference List. (Sample text– Add to and/or modify with information applicable to the study)

14. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A quality assurance representative from <<Rho (or a qualified delegate) or Sponsor>>, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits. (Sample text– Add to and/or modify with information applicable to the study)

15. ETHICS

15.1. Ethics Review

The investigator will not start this study, nor will investigational devices be shipped to the investigator's site, before providing <<Sponsor and/or Rho>> with evidence of <<IRB(s) or Ethics Committee(s)>> approval. The investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects. The investigator will not make any changes in the research without <<IRB(s) or Ethics Committee(s)>> approval, except where necessary to eliminate apparent immediate hazards to the subjects. The investigator will provide progress reports to the <<IRB(s) or Ethics Committee(s)>> as required by the <<IRB(s) or Ethics Committee(s)>>. The investigator will provide a final report to the <<IRB(s) or Ethics Committee(s)>> after completion of participation in the study. (Sample text– Add to and/or modify with information applicable to the study)

15.2. Ethical Conduct of the Study

The investigator should conduct the study in accordance with this protocol, the Declaration of Helsinki, and ICH GCP guidelines. The investigator and << Sponsor and/or Rho>> will sign the protocol and study contract to confirm agreement. The investigator will not implement any amendment (deviation or changes of the protocol) without agreement by <<Sponsor and/or Rho>> and the <<IRB(s) or Ethics Committee(s)>> approval/information, except where necessary to eliminate immediate hazards to study subjects or when changes involve only logistical or administrative aspects of the study. (Sample text– Add to and/or modify with information applicable to the study)

15.3. Written <<and/or Verbal>> Informed Consent/Assent

15.3.1. Subject Information and Informed Consent/Assent

The informed consent document will be approved by the <<IRB(s) or Ethics Committee(s)>> that is appropriate for each study site. The investigator is responsible for ensuring that the subject fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible. Verbal consent will be accepted for subjects who are unable to read or write. No subject should be obliged to participate in the study. Subjects, their relatives, guardians, or (if applicable) legal representatives must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the subject's subsequent care. Subjects must be allowed sufficient time to decide whether they wish to participate. Subjects will provide assent, while their parent(s) and/or legal guardian(s) will provide consent after they have read the Informed Consent/Assent Form and the Investigator or designee has answered any questions they may have about the study.

The subject must be made aware of and give consent <<or assent>> to direct access to his/her source medical records by study monitors, auditors, the <<IRB(s) or Ethics Committee(s)>>, and regulatory authorities. The subject should be informed that such access will not violate subject confidentiality or any applicable regulations. The subject should also be informed that he/she is authorizing such access by signing <<and/or giving assent to>> the informed consent form.

Each subject will be given a signed copy of the informed consent <<and assent>> form to keep for his/her records. (Sample text– Add to and/or modify with information applicable to the study; for example, emergency consent may be required in situations wherein the investigational product is used in the ER and the subject is unable to consent because they are unconscious;)

15.3.2. Provision of New and Important Information Influencing Subject's Consent and Revision of the Written Information

When any new and important information that may be relevant to the subject's consent is obtained, the investigator and <<Sponsor, Rho, and/or their designee(s)>> will consult with each other on how to deal with the information. When <<Sponsor, Rho, and/or their designee(s)>>, and a responsible investigator judge it necessary, the investigator must immediately provide the subjects with such information, revise the written information and other explanatory documents based on the new information, and obtain approval from the <<IRB(s) or Ethics Committee(s)>>. In this instance, the investigator should also immediately inform subjects currently participating in the clinical study of such information, confirm their intention to continue participation, re-explain the study to them using the revised written information and other explanatory documents, and obtain written consent to continue participation based on their voluntary decision. (Sample text– Add to and/or modify with information applicable to the study)

15.4. Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being. Each subject will be asked to complete a form allowing the investigator to notify the subject's primary health care provider of his/her participation in this study. (Sample text– Add to and/or modify with information applicable to the study)

16. ADMINISTRATIVE PROCEDURES

16.1. Publications of the Clinical Study

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to <<Sponsor>>. (Sample text– Add to and/or modify with information applicable to the study)

16.2. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the investigator, << Sponsor and/or Rho>> after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator, << Sponsor and/or Rho>>. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and <<Sponsor and/or Rho>>. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the <<IRB(s) or Ethics Committee(s)>> will be promptly notified.

No deviation from the protocol or investigational plan will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the sponsor, and the regulatory authorities (e.g., <<FDA and/or EMA>>) or the <<IRB(s) or Ethics Committee(s)>> if applicable, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to <<Sponsor and/or Rho>> and to the <<IRB(s) or Ethics Committee(s)>>, if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan. (Sample text– Add to and/or modify with information applicable to the study)

No waivers to inclusion/exclusion criteria will be granted; subjects need to meet all criteria, exactly as specified, to be enrolled. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a subject in an emergency. Deviations that occur unintentionally or are the result of action by the subject must be documented and reported to Ironshore and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

16.3. Data and Safety Monitoring Board or Data Monitoring Committee

A Data Safety and Monitoring Board (DSMB) will review accumulated individual safety data. The data to be reviewed will be <<blinded, partially blinded, or unblinded>>. The first DSMB meeting, other than the orientation meeting, will occur when X subjects randomized to the <<study drug or device>> group and X subjects randomized to the <<placebo or control>> group, X subjects total, have completed Day X of the study. Subsequent DSMB meetings will occur approximately <<e.g., every two weeks, monthly, or bimonthly>>. Should initial enrollment be slower than expected, the DSMB will have the option of reviewing data prior to the X subject/Day X event if the DSMB believes such a review would be of value. An earlier review would be in addition to the planned X subject/Day X review. Should any untoward safety issue be observed, or any of the stopping rules outlined in Section 5.5 be invoked, the DSMB will schedule an immediate meeting to review the relevant safety data. All DSMB members will be

independent of the Sponsor and study. Membership in the independent DSMB will consist of <<description of the number of members and relevant expertise of each member>>. (Sample text– Add to and/or modify with information applicable to the study; remove if not applicable for the study)

17. DATA HANDLING AND RECORD KEEPING

17.1. Inspection of Records

<<Sponsor and/or Rho>>, their designee(s), the <<IRB(s) or Ethics Committee(s)>>, or regulatory authorities will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow <<Sponsor and/or Rho>>, their designee(s), the <<IRB(s) or Ethics Committee(s)>>, or regulatory authorities to inspect the investigational <<drug or device>> storage area, investigational <<drug or device>> stocks, investigational <<drug or device>> records, subject charts and study source documents, and other records relative to study conduct. (Sample text– Add to and/or modify with information applicable to the study)

17.2. Retention of Records

The principal investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. (Sample text– Add to and/or modify with information applicable to the study)

17.3. Sample Retention

Samples may be used for purposes related to this research. The samples may be stored until the study team has determined that specimens are no longer needed and the decision has been made that there are no samples to be re-assayed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

18. REFERENCES

(Add references as applicable)

19. APPENDICES

(Add relevant appendices as applicable)