|  |  |
| --- | --- |
| **FULL TITLE:** | <Type here> |
| **Protocol No.** | <Type here> |
|  |  |
| **Sponsor:** | <Type here> [remove if Sponsor-Investigator study] |
| **Sponsor-Investigator:** | <Type here> [remove if Sponsor study and change to “Principal” or “Lead” Investigator |
| **Sub-Investigators / Collaborators:** |  |
| **Study Support/Funding:** | <Type here> |
|  |  |
| **ClinicalTrials.gov Identifier:** | <Type here> |
| **Other Identifying Numbers (if applicable):** | [remove row if not applicable] |
|  |  |
| **Version No.** | <Type here> |
| **Date:** | [dd-mmm-yyyy] |
|  |  |

|  |
| --- |
| **GCP Statement** |
| This clinical study will be conducted in accordance with applicable Health Canada regulations, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on current Good Clinical Practice (GCP), and the Declaration of Helsinki. |
|  |
| **Confidentiality Statement** |
| This clinical study protocol contains information which is of a confidential, trade-secret or proprietary nature. The protocol is for the use of [Sponsor or Sponsor-Investigator] and [his/her] designated representatives participating in the investigational trial. It is not to be disclosed to any other person or party without the prior written approval of [Sponsor or Sponsor-Investigator]. |

*GUIDANCE NOTE: If Sponsor for the study is an Investigator, Sponsor should be replaced throughout with Sponsor-Investigator (SI).*

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# **INVESTIGATOR AGREEMENT**

|  |  |
| --- | --- |
| **Protocol Title:** | <Type here> |
| **Protocol No.:** | <Type here> |
| **Version No.:** | <Type here> |
| **Date:** | <Type here> |

This clinical study will be conducted in accordance with applicable Health Canada regulations, ICH guidelines on current GCP, and the Declaration of Helsinki.

I confirm that I have read and understand this protocol and I agree to conduct this clinical study in accordance with the design and specific provisions of the protocol, with the exception of a change intended to eliminate an immediate hazard to participants. Any deviation from the study protocol will be documented in the case report form.

I agree to promptly report to the applicable ethics boards any changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without prior ethics and sponsor approval, except where necessary to ensure the safety of study participants.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| Name |  | Signature |  | Date (dd-mmm-yyyy) |

# **STUDY CONTACT DETAILS**

|  |  |
| --- | --- |
| **Role** | **Contact Details** |
| Medical Monitor |  |
| SAE Reporting |  |
| Study Support |  |
| Clinical Laboratory Facility |  |
| [Specimen] Analysis |  |
| Investigational Product Supply |  |
| [Other – study specific] |  |

*[Remove any roles that do not apply. Remove entire section if simple study design.]*

# **ABBREVIATIONS AND DEFINITONS**

*(Provide a list of abbreviations and definitions of unusual or specialized terms or measurement units used in the protocol. At the first appearance in the text – excluding summary - spell out abbreviated terms with the abbreviation indicated in parentheses.)*

|  |  |
| --- | --- |
| **Acronym / Abbreviation** | **Definition** |
| <Type here> | <Type here> |
| <Type here> | <Type here> |
| <Type here> | <Type here> |
| <Type here> | <Type here> |
| <Type here> | <Type here> |
| <Type here> | <Type here> |

# **PROTOCOL SYNOPSIS**

|  |  |
| --- | --- |
| **Full Title** |   |
| **Short Title** |  |
| **Protocol and Version No.** |  |
| **Clinical Phase** |  |
| **Study Duration** | Enrollment period:  |
| Study period: |
| **Sponsor/Sponsor-Investigator**  |  |
| **Number of Centres** |  |
| **Study Design** |  |
| **Primary Objective** |  |
| **Secondary Objectives** |  |
| **Exploratory Objectives** |  |
| **Sample Size** | N = |
| **Randomization** |  |
| **Study Population**  | [include diagnosis and/or main eligibility criteria] |
| **Investigational Product Description** | [if using marketed drug(s), include DIN or NHN] |
| **Control** |  |
| **Administration and Dosing** |  |
| **Duration of Treatment** |  |
| **Outcome Measures** | Primary: |
| Secondary: |
| Exploratory: |
| **Statistical Analysis** |  |

# **STUDY FLOW CHART**

*[Insert as applicable or remove heading if simple study design.*

*REMOVE IF NOT APPLICABLE]*

# **INTRODUCTION, BACKGROUND, AND STUDY RATIONALE**

*(Include background information for the study. The introduction should place the study in the context of current medical practice or the Investigational Product's clinical development. Provide all references [published and unpublished] used to support the material presented in the introduction using Author, date format. Where appropriate, include the subsections below.)*

## **[Disease, Condition or Other] Background**

*(Include relevant information about the disease, condition or other area of study. This may include a description of the disease pathology and natural history in the study population.)*

<Type here>

## **Current Treatment Options**

*(Discuss current medicines/treatment modalities used to treat the disease and their limitations.)*

*(Remove if discussed in Section 1.1)*

<Type here>

## **Summary of Previous Data with [Study Intervention/Investigational Product]**

*(Refer to the Investigator’s Brochure (IB), Product Monograph or Package Insert and discuss the nonclinical studies with potential clinical significance and clinical studies with relevance to the current study. Include the name and description of the Investigational Product.)*

(Remove if discussed in Sections 1.1 or 1.2 above.)

<Type here>

## **Potential Risks and Benefits to Human Participants**

*(List the potential benefits of the Investigational Product and provide a brief summary of the associated risks. A detailed discussion of potential risks and precautions should be provided in Section 7. Consult the IB, Product Monograph or Package Insert.)*

<Type here>

## **Study Rationale**

*(Provide a rationale for the study including, if applicable, its design.)*

<Type here>

# **STUDY OBJECTIVES AND DESIGN**

## **Overall Study Design**

*(Describe the overall study. Use schematic(s) or figure(s) as appropriate. The following information should be included:*

* *A description of the study type/configuration/level and method of blinding [e.g., open, single or double-blind, parallel groups]*
* *Level of control [e.g., observational, uncontrolled, controlled]*
* *Method of control [e.g., placebo, active, historical]*
* *Method of assignment to treatment*
* *A specific statement of the primary variable to be measured during the study*
* *Study participant population and number of participants to be included and, if known, number of planned study centres and countries*
* *A description of the study treatment[s] including both investigation product[s], placebo and/or comparator[s]*
* *The expected duration of participant participation, and a description of the sequence and duration of all study periods, including follow-up, if any.*
* *Include stopping rules, if applicable.)*

<Type here>

## **Primary Objective(s)**

*(State objective clearly and succinctly; use bullet/point form as appropriate.)*

<Type here>

## **Secondary Objective(s)**

*(State objective(s) clearly and succinctly; use bullet/point form as appropriate. Remove heading if study has no secondary objective(s).)*

<Type here>

## **Exploratory Objectives(s) *(Remove if not applicable)***

*(State objective(s) clearly and succinctly; use bullet/point form as appropriate.*

<Type here>

## **Sub-studies *(Remove if not applicable)***

*(Describe any sub-studies being conducted within the study. Include overall study design and objectives of each sub-study. Use a level 3 heading for each sub-study or combine under this heading, as appropriate.)*

<Type here>

# **SELECTION AND ENROLLMENT OF PARTICIPANTS**

## **Number of Participants**

*(List the number of participants planned to be enrolled in the study. List number of sites and countries if known. If sub-studies are included, list expected number of participants to be enrolled in each sub-study. Use level 3 headings for sub-studies as appropriate, e.g. 3.1.1 Sub-study #1.)*

<Type here>

## **Inclusion Criteria**

*(List criteria in order of importance. Start with age and sex, and primary diagnosis.)*

*(Sample text)*

1. [age and sex]
2. [primary diagnosis]
3. <Type here>

## **Exclusion Criteria**

*(List criteria in order of importance. Consider the following standard exclusion criteria.)*

*(Sample text)*

1. Participants with a known hypersensitivity/allergy to the [intervention].
2. Participants who are actively participating in an experimental therapy study or who have received experimental therapy within the last [XX weeks/months].
3. Participants who are a poor medical risk because of other systemic diseases or active uncontrolled infections.
4. <Type here>

## **Strategies for Recruitment**

*(Describe the planned strategies for achieving adequate participant enrollment to reach the target sample size.)*

<Type here>

## **Enrollment Procedures**

*(If applicable, describe specific procedures for enrollment. Otherwise remove heading.)*

<Type here>

## **Co-enrollment Guidelines *(Remove if not applicable)***

*(Describe applicable allowance/restrictions on enrollment in other research studies, if applicable.)*

<Type here>

## **Sub-study Enrollment Procedures *(Remove if not applicable)***

*(Describe any sub-studies that relate to the study. Indicate whether or not the sub-studies will have their own consent form.)*

<Type here>

## **Other *(Remove if not applicable)***

*(Use topic-specific heading, as applicable. Provide any additional information pertaining to selection and enrollment of participants.)*

<Type here>

# **WITHDRAWAL OF PARTICIPANTS**

## **Withdrawal criteria**

*(Include a statement of whether and how participants are to be replaced. Consider the following standard language; adjust accordingly based on study design.)*

*(Sample text)*

A participant may be withdrawn from the study due to the reasons listed below including, but not limited to:

* a new health condition appears that is suspected to require care or medications prohibited by the protocol
* it is in the participant's best interest according to the Investigator's clinical judgment
* the Sponsor terminates the study
* <Type here>

## **Procedures for Discontinuation**

*(Describe procedures to be followed. Refer to specific visit.)*

# **RANDOMIZATION AND BLINDING PROCEDURES**

*(If the protocol does not include Randomization and blinding procedures, include a statement indicating that here and delete sections 5.1 and 5.2. Otherwise include specific information in the sections below.)*

<Type here>

## **Randomization *(Remove if not applicable)***

*(Describe the Randomization ratio. Describe the Randomization number, including the meaning of embedded number subsets, if applicable. Include a description of the Randomization method and how it will be executed. Explain the method of generating random numbers (e.g. will study staff call a Randomization phone line, and if so, who will call the line [e.g. site pharmacist, study coordinator], use envelopes, etc.). Explain who will have access to the codes. If Randomization is stratified, include stratification information and justify the decision to stratify on the variables.)*

<Type here>

## **Blinding *(Remove if not applicable)***

*(Identify who is blinded and who is unblinded (if applicable). Describe specific procedures that will be used to carry out blinding [e.g., how containers were labeled, how IV lines were covered, sealed code list/envelopes], including circumstances in which the blind would be broken for an individual or for all participants [e.g., for SAEs]. Mention the procedures that will be used for breaking the blind. Describe the measures taken to ensure that the intervention and placebo will be indistinguishable. Sometimes blinding is attempted, but is known to be imperfect because of obvious Investigational Product effects in at least some of the participants. Identify such problems or potential problems and, if there will be any attempts to assess the magnitude of the problem or manage it, describe the action that will be taken.*

<Type here>

# **STUDY TREATMENTS**

## **Investigational Product Description**

Brand or Product Name: [insert]

Generic Name: [insert; if applicable]

DIN or NHN: [insert; if applicable]

*(Briefly describe product, including pharmacological class, indication and mechanism of action as applicable.)*

### **Expected Side Effects**

*(Summary of expected side effects from Product Monograph or Investigator’s Brochure. Bullet point list acceptable.)*

*(Use content-specific heading: e.g. [Product X] Formulation.*

<Type here>

### **Formulation, Storage and Handling**

*(Describe the Investigational Product (IP) form, and how it is supplied. Describe reconstitution procedures and other preparation for IP administration. Describe storage and handling conditions. State that IP should be stored in a secure, locked facility accessible only to authorized study personnel.)*

<Type here>

## **Comparative Treatment or Placebo *(Change heading text based on study)***

Product Name: [insert]

Generic Name: [insert; if applicable]

DIN or NHN: [insert; if applicable]

*(Briefly describe comparator product, including pharmacological class, indication and mechanism of action as applicable.)*

### **Expected Side Effects**

<Type here>

### **Formulation, Storage and Handling**

<Type here>

##

## **Packaging and Labelling**

*(Describe how product is package e.g. vials/tubes/containers/packages and how much is contained e.g. X number in blister pack, X mL, X mg/mL. State that the product will be labeled as Investigational Product in accordance with applicable regulations. Include listing of inactive ingredients if appropriate.)*

## **Study Product Supply and Accountability**

*(Describe how Investigational Product (IP) will be supplied, e.g. through pharmacy, and how IP accountability will be handled.)*

<Type here>

## **Dosing and Administration**

*(Describe the treatments to be administered to each arm of the study including name[s] of all product[s], dose[s], dosing schedule[s], route/mode[s] of administration, and the treatment period[s] including follow-up period for each individual participant. If the study is controlled, you can use separate subsections for the Investigational Product[s] and/or comparative treatment, if appropriate.)*

<Type here>

## **Dose Reduction or Modification *(Remove if not applicable)***

*(State any criteria or circumstances for dose reduction or modification, for safety reasons or other.)*

<Type here>

## **Concomitant Medications/Natural Remedies/Foods**

*(State any medication[s]/treatment[s] permitted, prior to and during the study.)*

*(Sample text)*

There are no restrictions on the use of concomitant medications in the study. Concomitant medications will be collected at study visits and recorded in the CRF.

<Type here>

## **Concomitant Alcohol and “Street” Drug Use *(Remove if not applicable)***

*(Describe in detail if alcohol or illicit drug use is allowed/restricted/prohibited during the study. Indicate whether or not alcohol/drug use is to be monitored, and the procedures to be used for such monitoring.)*

<Type here>

## **Prohibited Medications and Procedures *(Remove if not applicable)***

*(State any medication[s]/treatment[s] and procedures prohibited prior to and during the study.)*

<Type here>

## **Precautionary Medications and Procedures *(Remove if not applicable)***

*(State any medication[s]/treatment[s] and procedures that are precautionary prior to and during the study.)*

<Type here>

## **Prophylactic Medications and Procedures *(Remove if not applicable)***

*(State any medication[s]/treatment[s] and procedures that are precautionary prior to and during the study.)*

<Type here>

## **Rescue Medications *(Remove if not applicable)***

*(State any rescue medication[s]/treatment[s] permitted during the study.)*

<Type here>

## **Participant Access to Study Medication at Study Closure**

*(Describe if and how participants can access study medication at the end of study, including compassionate use or standard of care.)*

<Type here>

# **RISK MANAGEMENT**

## **Acceptable Methods of Birth Control *(Remove if not applicable)***

*(If applicable to population, describe acceptable methods of birth control.)*

*(Sample text)*

While abstinence from sexual activity is the only certain method to prevent pregnancy, female participants of childbearing potential who are or who anticipate the possibility of becoming sexually active with a male partner during the study and for X months after study completion must practice an acceptable method of contraception such as:

1. Double barrier methods (acceptable barrier methods include diaphragm, coil, contraceptive foam, sponge with spermicide, condom); or
2. Oral, injectable or implant contraceptives plus one barrier method; or
3. IUD plus one barrier method; or
4. A method of birth control considered acceptable by the trial physician.

Participants using hormone-based contraceptives (pills, injection or implant) must have used them consistently for a minimum of 30 days before the start of the study.

Male participants who are or anticipate the possibility of becoming sexually active during the study and for X months after study completion must practice an acceptable method of contraception such as:

1. Previous vasectomy; or
2. Use of a condom plus spermicide, plus relationship with a female partner who practices an acceptable method of contraception (see above).

Contraceptive measures will be reviewed with participants at all study visits over the course of the study.

## **Mental Health Support *(Remove if not applicable)***

*(If applicable, describe any mental health support that will be provided during the trial either routine or due to an event/diagnostic information.)*

<Type here>

## **Risk Management**

*(Describe the steps that will be taken to minimize risk in study.)*

*(Sample text)*

Risk minimization, management, and assessment procedures have been implemented in the study to minimize and assess potential risks to participants who participate in this clinical study with [*insert Investigational Product*]. Components include: (1) specific study entry and exclusion criteria to ensure that participants who have underlying characteristics that potentially increase their risk for an adverse outcome are excluded [*modify accordingly based on protocol*]; (2) protocol-specific procedures for minimizing and managing certain AEs, such as [*list examples*]; (3) overview surveillance by an independent Data Safety Monitoring Committee [*if applicable*]; (4) ongoing follow-up (X months total) for safety monitoring purposes [*if applicable*]; (5) [*list additional as applicable to the study*].

# **CLINICAL AND LABORATORY EVALUATIONS**

## **Clinical Evaluations**

*(Describe in detail the clinical evaluations that will be done in the study* *(e.g. medical history, medication history, physical exam, questionnaires, ECG's, biopsies, etc..))*

*See Section 9.1 Table XX: Schedule of Events*

## **Laboratory Evaluations and Specimen Collection *(Remove if not applicable)***

*(If clinical laboratory tests are to be done, include a table or summarize in paragraph form using subheadings as appropriate. Tests should be specific to your study and may or may not include all parameters listed in Table 1.)*

*(This section should also describe the various research assays to be employed in the study.)*

**Table 1: Clinical Laboratory Tests (Remove if Not Applicable)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Hematology** | **Serum Chemistry** | **Urinalysis** | **Serology** | **Illicit Drugs** | **Other** |
| * <Type here>
 | * <Type here>
 | * <Type here>
 | * <Type here>
 | * <Type here>
 | * <Type here>
 |

*(Describe how specimens are to be collected e.g. standard-of-care through local labs, collected, processed and stored on-site, a mixture of the two, etc..)*

<Type here>

## **Questionnaires and/or Scales *(Remove if not applicable)***

*(Describe any questionnaires and scales to be used in the study. Section should be subdivided into questionnaires and scales administered or completed by:*

* *Study staff*
* *Study participants*

*as applicable.*

*As much as possible, questionnaires and scales should be validated and references provided accordingly. If study-specific questionnaires or scales are used, each must be included as an Appendix and cross-referenced in this section.)*

<Type here>

## **Stored Research Specimens and Plans for Possible Future Testing *(Remove if not applicable)***

*(Describe what samples are to be stored for future use, where and for what type of testing/use, if known. Indicate if genetic testing will be performed. Indicate if the specimens may be used in any other research under this or other protocols for which separate signed informed consent documents will be obtained. Indicate whether or not lab materials are being supplied (e.g. are blood tubes, slides, labels, cryovials, shippers, etc. being supplied by the sponsor, or does the site have to provide any of these items?).*

<Type here>

# **STUDY PROCEDURES**

## **Schedule of Events**

*(Include the schedule of procedures/assessments in this section. See example below – consider landscape orientation if study contains numerous visits. Table should match the assessments described in the text.)*

**Table 2: Schedule of Events**

|  |  |  |
| --- | --- | --- |
| **Visit Type** | **Screening** | **Study Visits** |
| **Baseline** |  |  |  | **End of Tx** | **Safety Follow-up** |
| **Visit Window** **Procedures:**  | **-4 to 0 weeks** | **D1, W1** |  |  |  |  |  |
| Informed Consent | X |  |  |  |  |  |  |
| Eligibility Assessment | X |  |  |  |  |  |  |
| Medical History |  |  |  |  |  |  |  |
| [insert study-specific] |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Adverse Events  |  | X |  |  |  | X | X |
| Concomitant Medications |  | X |  |  |  | X | X |

[footnotes]

## **Screening Visit (-4 to 0 weeks)**

*(Describe procedures to be done at screening visit. Indicate the study visit window related to the Baseline/Randomization visit as well as the amount of time the visit will require. Use bullet points.)*

<Type here>

* <Type here>

## **Baseline Visit (Day 1, Week 1)**

*(Describe procedures to be done at baseline visit. and indicate the time required. If the Randomization visit is separate from the Baseline visit, then describe in detail all procedures required for EACH visit.)*

<Type here>

* <Type here>

## **Visit [no.] (Day X, Week X)**

<Type here>

* <Type here>

*[Add further Visit numbers based on Schedule of Events]*

## **Final Treatment Visit**

*(Describe procedures to be conducted at the final treatment study visit.)*

<Type here>

* <Type here>

## **Safety Follow-up Visit**

*(Describe procedures to be conducted at the safety follow-up visit.)*

<Type here>

## **Early Termination Visit**

*(Decribe procedures to be conducted at the early termination visit. This visit should include all procedures to be conducted at the final study visit. If procedures are the same as the final study visit, simply cross-reference to the appropriate section. Any specific early termination visit procedures should be listed in this section. Indicate if there will be a 30-day post follow-up safety visit for participants who stop the trial early.)*

<Type here>

## **Re-contact of Participants after Trial Termination**

*(Describe circumstances, rationale and procedure for re-contacting participants after trial termination, if applicable.)*

<Type here>

# **EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS**

## **Definitions**

### **Adverse Event (AE)**

*(Sample text)*

An AE is any untoward medical occurrence in a patient or clinical investigation participant, administered a study medication/intervention, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) study medication/intervention, whether or not related to the medicinal (investigational) study medication/intervention.

During each follow-up visit with the participant, information on AEs will be gathered and documented accordingly. AEs will be graded as mild, moderate, severe or life-threatening and assessed by causality as probably related, possibly related, unlikely to be related or not related to the *[Investigational Product (Arm X only)*].

Stable chronic conditions which are present prior to clinical trial entry and do not worsen are not considered AEs and will be accounted for in the participant’s medical history.

### **Serious Adverse Events (SAEs)**

*(Sample text)*

An SAE is defined as an AE meeting one of the following criteria at any dose:

* Results in death during the period of protocol-defined surveillance
* Is a life-threatening event (defined as a participant at immediate risk of death at the time of the event)
* Results in in-patient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance
* Results in persistent or significant disability or incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
* Is a congenital anomaly or birth defect

Any other important medical event that may not result in one of the above outcomes, may be considered a SAE when, based upon appropriate medical judgment, the event 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 in-patient hospitalization, or the development of drug dependency or drug abuse.

Participants will be monitored during the XX-week study period for SAEs. If an SAE is ongoing at the time a participant discontinues/completes the study, the SAE will be followed until the Investigator agrees that the event is satisfactorily resolved, becomes chronic, or that no further follow-up is required.

## **AE Descriptions and Recording**

### **Intensity**

*[Describe the intensity (severity) scale that will be used for grading of AEs. The type of scale chosen should be relevant to the research being conduct. Common scales include:*

* *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (*[*http://rsc.tech-res.com/document/safetyandpharmacovigilance/table\_for\_grading\_severity\_of\_adult\_pediatric\_adverse\_events.pdf*](http://rsc.tech-res.com/document/safetyandpharmacovigilance/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf)*).*
* *Common Terminology Criteria for Adverse Events (CTCAE) (https://ctep.cancer.gov/protocolDevelopment/electronic\_applications/ctc.htm)]*

### **Relationship to Study Treatment**

*(Sample text)*

For all collected AEs (including SAEs), the clinician who examines and evaluates the participant will determine the AE’s causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

**Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to Investigational Product administration and cannot be explained by concurrent disease or other products or chemicals. The response to withdrawal of the product (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

**Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the Investigational Product, is unlikely to be attributed to concurrent disease or other products or chemicals, and follows a clinicallyreasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

**Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an adverse drug event may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.

**Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to Investigational Product administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other products or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).

**Not related:** The AE is completely independent of Investigational Product administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

## **Reporting and Evaluation of SAEs and Other Clinically Significant AEs**

### **SAEs**

*(Sample text)*

All SAEs which occur during the course of the study must be reported to [insert name of organization] within 24 hours of the site becoming aware of the event. [CTN or CHÉOS or Sponsor/Sponsor-Investigator] will be responsible for reporting SAEs to Health Canada on behalf of the Sponsor/Sponsor-Investigator (*choose* *appropriate title*)].

SAEs will be reported to:

|  |
| --- |
| **[insert name of organization]** |
| Attention: | (Project Manager) |
| Phone:  | <Type here> |
| Fax:  | <Type here> |
| E-mail:  | <Type here> |

### **Other Clinically Significant AEs (if applicable)**

*(This is a protocol-specific section; remove heading if not needed.)*

## **Events Due to Disease Progression (if applicable)**

*(This section is to be used only when disease progression is expected to result in a large number of AEs that may confound the study* ***and*** *the study is blinded.)*

*(Sample text)*

Events that are judged to be unequivocally due to disease progression should be recorded in the source documents, but not reported as AEs. Accordingly, events that meet the criteria of SAEs (refer to Section 10.1.2) but that are judged unequivocally due to disease progression should not be reported as SAEs. For example, if a participant is hospitalized or dies due to unequivocal disease progression, the events associated with the disease progression should not be reported as SAEs.

## **Follow-up for Adverse Events**

*(Sample text)*

Any AE that occurs between the time that a study participant is randomized and the time that s/he departs the study at the end of the final study visit (or at the time of early discontinuation of the participant from the study for any reason) will be captured and recorded. At each contact with the participant, the investigator (or designate) must seek information on AEs by specific questioning and, as appropriate, by examination*.*

AEs that had previously been reported by the study participant will also be reassessed for duration, intensity and possible reoccurrence. Assessment of safety will include clinical observation and monitoring of *[list specific testing]*.

All AEs (including SAEs) will be followed until resolution or until the investigator and the clinical/medical monitor are in agreement that the AE has resolved, stabilized or become chronic and no further follow-up is required.

## **Pregnancy Follow-up**

*(This section is to be used when applicable for the study (e.g., it will not apply to studies that include only men, and it will likely not apply to studies in elderly populations. Sample text is as follows.)*

If a participant becomes pregnant during the study, the Investigator must inform the Sponsor and collect follow-up data regarding the pregnancy, birth, and status of the child. The Sponsor will provide special CRFs for data collection in the case of pregnancy. Follow-up should be continued until study close-out at the study centre. After close-out, the Sponsor will continue to obtain follow-up information.

Pregnancy should be recorded as a protocol deviation if it is included in the exclusion criteria. Pregnancy is not an adverse event; however, any complication related to pregnancy would be considered an adverse event. Refer to Section 10.1.2.

# **STATISTICAL CONSIDERATIONS**

## **General Study Design**

*(Describe the study design characteristics that are relevant to the statistical considerations.)*

<Type here>

## **Sample Size Considerations/Justification**

*(Specify how the sample size for the study was determined. The endpoint used in any calculations should be stated as well as any assumptions regarding the variability, prevalence, relative difference between groups, etc. in the outcome. Provide calculations for a range of values when the input values are highly uncertain. Statistical power, precision of estimates and assumed type I error rate should be provided if relevant. In addition, adjustments to the sample size to account for loss to follow-up and sensitivity analyses to the assumptions used in the calculations should be described. Some support, ideally in the form of references, must be given to justify assumptions made in the sample size calculations.*

*For comparisons of two proportions, the actual proportions must be stated. The difference between proportions is inadequate for the reviewer to assess the sample size calculation. Similarly, for time-to-event calculations, the relevant parameter (hazard rate, median time to event) in each arm should be stated. In addition, assumptions about crossover, dropout from treatment and loss to follow-up should be stated. Even if it is the case that the stated difference between treatments for which the study is powered is meant to reflect what would happen even with these variables taken into account, it is important to indicate expectations since a considerable excess of such occurrences may lead to a difference between treatment lower than anticipated. Such variables should be closely monitored by the DSMC.*

*An estimate of the length of time required to complete the enrollment of patients should also be provided here.)*

<Type here>

## **Endpoints/Outcome Measures**

*(Describe endpoints / outcomes in order of importance e.g. primary, secondary, exploratory etc. If there are multiple endpoints within heading, rank numerically in order of statistical importance.)*

*(Sample Text)*

Primary Endpoint:

1. <Type here>

Secondary Endpoints:

1. <Type here>
2. <Type here>

### **Analysis of Primary Outcome Measures**

*(Describe analysis of the primary outcome measure(s). Indicate which participants will be included (e.g. all randomized participants) in the analysis and how loss-to-follow-up and missing data will be handled. List covariates that will be included as adjustment variables or describe the procedure that will be used to select these variables. Describe any sensitivity analyses that will be conducted.)*

<Type here>

### **Analysis of Secondary Outcome Measures**

*(Describe analysis of the secondary outcome measure(s), if applicable.)*

<Type here>

### **Analysis of Exploratory Outcome Measures *(Remove if not applicable)***

*(Describe analysis of exploratory outcome measure(s), if applicable.)*

<Type here>

## **Summary of Demographic and Baseline Data**

*(Describe how demographic and baseline data will be summarized.)*

<Type here>

## **Planned Subgroup Analyses *(Remove if not applicable)***

*(Remove heading if no subgroup analyses are planned.)*

*(Any subgroup analyses that are planned should be described in this section; these analyses might include subgroup analyses of primary or secondary endpoints, or even other interesting subgroup questions that the study team might want to investigate using the trial data. Endpoints, subgroup definitions and intended statistical methodology should all be specified.)*

<Type here>

## **Interim Analyses *(Remove if not applicable)***

*(Remove heading if no interim analyses are planned.)*

*(If there are planned interim analyses of the study data, they should be described in this section. Some of the details that should be provided include the schedule of analyses (e.g. at ¼, ½ and final enrollment), how the type I error will be distributed across the various analyses (e.g. spending function for the “alpha”), what outcomes will be examined at interim analyses, and what statistical tests will be used. In addition, details regarding the distribution list for the interim results should be provided as well as a brief discussion of the possible consequences of these analyses (e.g. will the trial potentially be stopped due to efficacy [or lack thereof] or only if there is a safety concern, futility, etc..))*

<Type here>

## **Other Considerations**

*(In this section, details related to any anticipated analytical issues should be provided. Some examples of items that could be clarified beyond the level of detail given in the sections above might include:*

* *Acceptable windows around visits for inclusion of data into “by visit” summaries could be defined (e.g. visit date +/- 2 weeks)*
* *An outline of any data requiring a blinded review prior to un-blinding and analysis; responsibilities for this task could be described*
* *How potential differences between equipment at different sites might be addressed.)*

<Type here>

# **STUDY ETHICAL CONSIDERATIONS**

## **Ethical Conduct of the Study**

*(Sample text)*

This study will be conducted in accordance with the ICH-GCP Guidelines, applicable regulations (*insert specific regulations*) and the principles in the Declaration of Helsinki. The Investigator will be thoroughly familiar with the appropriate use of the study treatment as described in the protocol and [*insert product labeling e.g. IB, package insert, product monograph*].

## **Informed Consent**

*(Sample text)*

All participants will be given detailed oral and written information about the study. Consent forms describing in detail the study medication/intervention(s) study procedures and risks will be given to each participant and written documentation of informed consent is required prior to starting study medication/intervention. Participants must sign an informed consent document that has been approved by a participating centre’s REB/IRB prior to any procedures being done specifically for the trial. Each participant should have sufficient opportunity to discuss the study, have all of their questions addressed and consider the information in the consent process prior to agreeing to participate. Participants may withdraw consent at any time during the course of the study without prejudice. The informed consent form will be signed and dated by the participant and the investigator or delegate. The original signed informed consent form will be retained in the participant’s study files and a copy will be provided to the participant.

The informed consent process must be conducted, and form signed before the participant undergoes any screening procedures that are performed solely for the purpose of determining eligibility for the study.

## **Confidentiality**

*(Sample text)*

All participant-related information including Case Report Forms, laboratory specimens, evaluation forms, reports, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only accessible to research staff. Participants will be identified only by means of a coded number specific to each participant (refer to Section 5). All computerized databases will identify participants by numeric codes only, and will be password protected.

Upon request, and in the presence of the investigator or his/her representative, participant records will be made available to the study sponsor, monitoring groups representative of the study sponsor, representatives of funding groups, and applicable regulatory agencies for the purpose of verification of clinical trial procedures and/or data, as is permissible by local regulations.

## **Institutional Review Board, Ethics Committee, or Research Ethics Board**

*(Sample text)*

The IRB, Ethical Committee or REB will review all appropriate study documentation to safeguard the rights, safety, and well-being of the participants. The study will be conducted only at sites where ethics approval has been obtained. A copy of the protocol (including protocol amendments), all versions of informed consent forms, other information to be completed by participants such as survey instruments or questionnaires, and any proposed advertising/recruitment materials must be reviewed and approved by the REB/IRB of each participating centre prior to implementation of the trial. The investigator will be responsible for obtaining REB/IRB approval of the annual Continuing Review throughout the duration of the study. The investigator will notify the REB/IRB of serious adverse events as applicable. The investigator will seek prior ethics approval for any protocol deviations except when the change is intended to eliminate an immediate hazard to participants. In this case, the protocol deviation will be promptly reported.

# **General Trial Conduct Considerations**

## **Adherence to Protocol**

### **Protocol Amendments**

*(Sample text)*

All protocol amendments will be reviewed and approved and if applicable submitted to the applicable regulatory agencies for prior approval or notification. The Investigator must sign and date the amendment prior to implementation. All protocol amendments must also be submitted to the ethics committee.

### **Protocol Deviations**

*(Sample text)*

No deviations from this protocol will be permitted without the prior written approval of the Sponsor, except when the modification is needed to eliminate an immediate hazard or hazards to participants. Any deviations that may affect a participant’s treatment or informed consent, especially those increasing potential risks, must receive prior approval from the REB unless performed to remove an immediate safety risk to the participants. In this case it will be reported to the REB and the Sponsor immediately thereafter. Any departures from the protocol must be documented.

## **Monitoring & Auditing**

### **Data Safety Monitoring Committee**

*(Remove heading if a DSMC will not be used for study or state why it is not required/ethical to include DSMC.)*

*(Describe the general composition of the DSMC as well as their role in the study. Some details to provide might include the frequency of DSMC reviews, proposals as to what data they will review and what recommendations the trial management team might expect them to make based on their review of the study data (e.g. stopping the trial due to safety concerns, lack of enrollment, etc.).)*

<Type here>

### **Study Monitoring**

*(Sample text)*

Each study site agrees to allow monitors from XXX and/or their representatives (CRO) direct access to the study records and medical records from those patients enrolled in the clinical study as well as Investigational Product accountability records. Adequate monitoring space and time must be provided for the Clinical Research Associates. The Sponsor will perform ongoing study site monitoring at X- to X-week intervals during enrollment to ensure quality assurance. Once enrollment is complete, the study site monitoring will be performed at X- to X-week intervals.

Protocol deviations will be monitored and recorded by the Sponsor. Details regarding patient accrual and ineligibility are specified in a separate, written Clinical Study Agreement between XXX and the Institution and Investigator.

### **Early Termination of the Trial**

*(Describe the conditions that would consistitute an early termination of the trial.)*

<Type here>

## **Record Keeping**

### **Data Collection**

*(Describe how data will be collected and if different systems will be used to capture different data points, e.g. electronic data capture vs. paper-based CRFs. Discuss any data transfers between the study site, CRO/labs, sponsor and/or CHÉOS/CTN.)*

*(Sample text)*

The Investigator must maintain detailed records on all study participants. Data for this study will be recorded in the participant’s chart and entered into CRFs. Applicable data from the participant’s chart should be recorded in the CRFs completely and promptly, taking time to correct any mistakes. Copies of CRFs will remain at the clinical site at the conclusion of the study.

<Type here>

### **Data Corrections**

Corrections of data entered on original CRFs must be made in the following manner:

* <Type here>

### **Source Documents**

*(Sample text)*

The Investigator must maintain adequate and accurate source documents upon which CRFs for each participant are based. They are to be separate and distinct from CRFs except for cases in which the Sponsor has pre-determined that direct data entry into specified pages of the participant’s CRF is appropriate. These records should include detailed notes on:

* Oral and written communication with participant regarding the study treatment (risks/benefits)
* Participation in trial and signed and dated informed consent forms
* Inclusion and exclusion criteria details
* Visit dates
* Adverse events and concomitant medication
* Results of relevant examinations
* Laboratory printouts
* Participant’s exposure to any concomitant therapy (start/stop dates, dosing details)
* Reason for premature discontinuation (if applicable)
* Enrollment number
* Methods of contraception and fertility status (if applicable)
* Compliance/non-compliance protocol deviation information

### **Data Management**

*(Sample text)*

Instructions concerning the recording of study data on CRFs will be provided by [insert group responsible]. Each study site is responsible for submitting the data in a timely fashion.

*[Provide additional study-specific details here]*

Detailed aspects of data handling will be described in the Data Management Plan.

### **Record Retention**

*(Describe the requirements and procedures for retaining study records. Note only regulatory studies require record retention for 25 years. For non-regulated studies, consult local REB/IRB and Institutional requirements for record retetion timelines.)*

*(Sample text – Regulated Studies ONLY)*

The Investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for 25 years, in accordance with applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and the Sponsor notified. The Investigator should ensure that no destruction of medical records occurs without the written approval of the Sponsor.

## **Other Services *(Remove if not applicable)***

*(Describe use of any other study management group e.g. steering committee, study advisory committee or other services, if applicable.)*

<Type here>

# **Disclosure and Publication Policy**

*(Describe plans for publication and authorship rules.)*

<Type here>

# **REFERENCES**

*(use full citation)*

<Type here>

<Type here>

<Type here>

# **APPENDICES**

*(Study-specific; include questionnaires, grading/rating scales etc.)*