**TransCelerate Common Protocol Template v10**

**About This Template**

**Disclaimer**

This document is a common protocol template. It contains sections marked as common text that may be used across protocols with little to no editing if the user chooses to do so. The use of this template is at the discretion of the user. Recommendations for modifications in future releases of the common protocol template can be submitted at any time and will be reviewed on a routine basis.

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**Components of the Protocol Template**

* The **Core Backbone** contains protocol information common to all phases, study populations, and therapeutic areas. The core backbone is streamlined and focused on the sites’ needs.
* **Libraries** group and store content that will be inserted into the core backbone and contain specific information related to therapeutic area, study intervention, country, and study population (eg, patient, healthy volunteer). For pediatric or adult/pediatric studies, include the content contained in the pediatric library.
* **Appendices** provide additional information that can be accessed when needed (eg, abbreviations, standard content regarding adverse event [AE] definitions).

**Core Backbone Headings**

* Level 1 and 2 headings should be consistent across protocols that use the CPT for reference and mapping purposes. The structure of this template was chosen to maximize alignment with the structure of the United States National Institutes of Health (NIH) and Food and Drug Administration (FDA) Clinical Trials Protocol Template.
* Level 1 and 2 headings should not be deleted. If they are not relevant to the study, not applicable should be inserted so that the numbering of subsequent sections is not changed.
* Level 3 and subsequent headings are suggested and can be deleted/added/modified as needed with the exception of those in Section 8.4 relating to Adverse Events, which are International Council for Harmonisation (ICH)-/regulatory agency-required wording and must be included.

**Terminology**

* The following terminology has been selected for use within TransCelerate common templates (protocol, statistical analysis plan [SAP], and clinical study report [CSR]) and is considered to be appropriate for all phases, study populations, and therapeutic areas.
  + *Participant* is used rather than subject, healthy volunteer, or patient when referring to an individual who has consented to participate in the clinical study. *Patient* or *individual* is used to describe the population represented by the study participants. All references to male & female pertain to sex assigned at birth, most often based on the infant’s physical characteristics.
  + *Study intervention* is used rather than study drug. *Study interventions* are all pre-specified, investigational and non-investigational medicinal products\*, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term. Investigational interventions are a subset of study interventions that are being tested or used as a control (eg, placebo or active comparator).

\* Refer to Eudralex - Volume 10 - Clinical trials guidelines (Chapter III) for further information on some categories of medicinal products which are normally used in clinical trials as NIMPs, such as rescue medication, challenge agents, medicinal products used to assess endpoints in the clinical trial, concomitant medicinal products systematically prescribed to the study participants, and background treatment. Of note, all products administered during the study that are not study interventions are recorded as “concomitant therapy”.

* + *Effectiveness* is used for medical device studies whereas for drugs, *efficacy* is used. The template should be updated as appropriate.

**Formatting and Text Conventions**

* Common Text: Black font preceded by *<Start of common text>* and followed by *<End of common text>* is common language intended to be harmonized across protocols. The recommendation is to use this text as written to maintain consistency across template users, but the text can be adapted or deleted if required. **Driver:** Industry regulation or guidance.
* Suggested Text: Black text preceded by *<Start of suggested text>* and followed by *<End of suggested text>* is suggested language that can be adapted or deleted as needed. Authors should consider implications to reuse within the CTS or for CT Registry if text is to be modified or removed.
* Variable Text: Blue bracketed text is variable text that should be addressed based on individual study needs.
* Example Text: Green italicized text preceded by *<Start of example text>* and followed by *<End of example text>* should be removed by the author if not utilized.
* Instructional Text: Is intended to aid in authoring of the protocol in this template. In the Basic Word Edition, it is red, hidden text, and paragraph marks must be enabled in order for it to be displayed. When attempting to access instructional text from the Basic Word Edition for use outside of the template (eg, hyperlinks), the content will need to be converted from hidden to unhidden text for it to be visible in other applications. In the Technology-enabled Edition, it will appear only in the Instructional Text panel.

The flags for the start and end of common, suggested, or example text can be removed automatically at the time of CPT finalization if the eCPT template has been used or should be removed manually by the author if the Basic Word Edition CPT template has been used.

All language proposed in this template (whether proposed as common, suggested, example, or variable text) may be modified as the user sees fit or as required by any applicable law or regulation.

**Guidance for Complex Study Designs**

* The following terminology has been selected for use for complex trials:
  + Master Protocol: The document which describes the overall clinical study design applicable to all related interventions or populations such as the clinical study rationale, objectives, endpoints, benefit-risk assessment, shared procedures regarding safety monitoring and reporting, and a common screening platform dictating participant eligibility and/or treatment allocation (CTFG, 2019). Sub-protocol: The document which describes the specific features of an intervention-specific or sub-population/disease-specific sub-study. Each intervention or population may have a separate sub-protocol.
  + Together, a master protocol and sub-protocol(s) define all the elements needed to conduct a study.
* Separate CPT documents should be used to capture all the details of the master protocol and each associated sub-protocol.
* For protocol sections not being utilized provide a reference to the content location. (eg, “Intervention details can be found in the master protocol/sub-protocol…”) or NA if not applicable. Avoid unnecessary duplication of information whenever possible.

Title Page

**Protocol Title:**

Protocol Title: The protocol should have a descriptive title that identifies the study sufficiently to ensure it is immediately evident what the study is investigating and on whom, and to allow retrieval from literature or internet searches.

For complex trials include a reference to the master protocol in each sub-protocol title.

**Example:**

A parallel-group treatment, Phase 2, double-blind, 2-arm study to investigate the safety and effectiveness of Addiryn tablets in decreasing agitation compared with placebo tablets in male and female participants aged 60 to 85 years of age inclusive with Alzheimer’s disease.

A structured title should contain details of participants, study interventions (and acronyms if relevant), comparison groups, outcomes, and study design. Use of the terms below will ensure alignment with Clinical Trials Registry Data Element Definitions.

Enter values from the list given for each of the indicated fields to complete.

**Intervention Model:**

* Single Group: Clinical studies with a single arm
* Parallel Group: Participants are assigned to one of two or more groups in parallel for the duration of the study.
* Crossover: Participants receive one of two (or more) alternative interventions during the initial period of the study and receive the other intervention during the second period of the study.
* Factorial: Two or more interventions, each alone and in combination, are evaluated in parallel against a control group.
* Sequential: Groups of participants are assigned to receive interventions based on prior milestones being reached in the study, such as in some dose escalation and adaptive design studies.

**Primary Purpose:**

* Treatment: One or more interventions are being evaluated for treating a disease, syndrome, or condition.
* Prevention: One or more interventions are being assessed for preventing the development of a specific disease or health condition.
* Diagnostic: One or more interventions are being evaluated for identifying a disease or health condition.
* Supportive Care: One or more interventions are evaluated for maximizing comfort, minimizing side effects, or mitigating against a decline in the participant’s health or function.
* Screening: One or more interventions are assessed or examined for identifying a condition, or risk factors for a condition, in people who are not yet known to have the condition or risk factor.
* Health Services Research: One or more interventions for evaluating the delivery, processes, management, organization, or financing of healthcare.
* Basic Science: One or more interventions for examining the basic mechanism of action (for example, physiology or biomechanics of an intervention)
* Device Feasibility: An intervention of a device product is being evaluated in a small clinical study to determine the feasibility of the product, or a clinical study to test a prototype device for feasibility and not health outcomes. Such studies are conducted to confirm the design and operating specifications of a device before beginning a full clinical study.
* Drug-device combination product: Studies evaluating the efficacy of an investigational drug and the use of medical devices as delivery system for this drug.
* Other: None of the other options applies

**Study Phase:**

See definitions under the heading for Study Phase and enter same phase in each place.

**Blinding**

Insert/copy definition from Overall Design section.

**Number of Arms**:

Numeric value for the number of arms in the study

**Health Measurement/Outcome:**

What is the primary outcome as given in the objectives being examined to determine the effect from the intervention? This should be included in the protocol title written in lay language, eg, measure the reduction in bad cholesterol; other potential terms: treat, delay, confirm, predict, identify, reduce, correct, reverse, lower, decrease, increase, or improve. Ensure this is written as an action/verb.

**Intervention Name**:

Enter a generic (international nonproprietary name [INN]) or trade name if required as per chemistry, manufacturing, and controls (CMC), if applicable.

**Intervention Form:**

eg, tablet, ampule, capsule, pill, patch, cream, ointment

**Participant Sex:**

eg, male, female, male and female

**Participant Age Range:**

eg, 18-65 years of age, 10-18 years of age

**Condition/Disease:**

The disease, disorder, syndrome, illness, or injury, etc that is being studied.

<Start of suggested text>

A(n) [intervention model] [primary purpose], [study phase], [blinding] [number]-arm study to investigate [health measurement/outcome] with [investigational intervention] [intervention form] compared with [investigational intervention] [intervention form] in [male and/or female] participants [X to X years of age] with [condition/disease]

<End of suggested text>

**Protocol Number:** [protocol number]

**Amendment Number:** [amendment number]

**[Amendment Scope:** Global/Country-specific/Regional]

**[Country/Region Identifier:** ISO-3166 country identifier]

**Compound:** [number or name]

**Brief Title:**

<Start of suggested text>

A study to investigate [health measurement/outcome] with [investigational intervention] [intervention form] compared with [investigational intervention] [intervention form] in participants aged [X to X years of age] with [condition/disease]

<End of suggested text>

Short title should be sufficiently detailed to make clear to a lay reader (reading level of 11-13 years) what the study is about and suitable for use as the Brief Title in ClinicalTrials.gov and for use with informed consents and ethics committee submissions.

Based on NIH expectations and public preferences, the optimal Brief Title on ClinicalTrials.gov includes the following data elements: condition/disease, health measurements/observations, intervention name, intervention form, participant age range, and participant sex.

Definitions of these terms are in the guidance following the additional details section.

Additional details:

* Reference to *participants* as the preferred term
* All abbreviations are defined.
* Does not end with a period.
* Technical study design terms are avoided.
* Limited to 300 characters

Study Phase: [study phase]

Please select one of the values for this field:

* N/A: for studies without phases (eg, studies of devices or behavioral interventions)
* Early Phase 1: exploratory studies, involving very limited human exposure, with no therapeutic or diagnostic intent (eg, screening studies, microdose studies)
* Phase 1: includes initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.
* Phase 1/Phase 2: for studies that are a combination of Phases 1 and 2
* Phase 2: includes controlled clinical studies conducted to evaluate the effectiveness of the intervention for a particular indication or indications in participants with the disease or condition under study and to determine the common short-term side effects and risks.
* Phase 2/Phase 3: for studies that are a combination of Phases 2 and 3
* Phase 3: studies conducted after preliminary evidence suggesting effectiveness of the intervention has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the intervention.
* Phase 4: studies of FDA-approved interventions to delineate additional information including risks, benefits, and optimal use.

**[Acronym]**:

Acronym or abbreviation used publicly to identify the clinical study, if any.   
Limit: 14 characters. Delete if not applicable.

**Sponsor Name:**

For complex trials there may be more than 1 identified sponsor.

Consider also listing the entity responsible for the management of the complex trial if different from the sponsor.

Legal Registered Address:

The sponsor name and legal registered address must be included. Consider not to include the name and function of the representative of the sponsor authorized to sign the protocol or any substantial modification to the protocol. Consider adding a statement that to ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Provide details separately.

In some countries, the clinical study sponsor may be the local affiliate company (or designee). If applicable, the details of the alternative sponsor and contact person in the territory should be provided to the relevant regulatory authority as part of the clinical study application and should not be included in the protocol.

[**Manufacturer]**: [insert manufacturer]

For device studies only:

Manufacturer is required for device protocols and may be deleted for other protocols. If the manufacturer is other than the sponsor, add manufacturer’s address.

Regulatory Agency Identifier Number(s):

Include all numbers that are applicable for the study and available at the time of protocol or amendment finalization, eg, investigational new drug (IND) number (include the center number, IND/IDE number, serial number), World Health Organization (WHO) universal trial number, European Clinical Trials Database (EudraCT, EU CT) number, ClinicalTrials.gov. Add type and number as applicable, it should be consistent between the Title Page and the Synopsis

|  |  |
| --- | --- |
| **Registry** | **ID** |
|  |  |
|  |  |

[Pediatric Investigational Plan Number]

Include pediatric investigational plan and/or pediatric study plan number(s), as applicable. This should be consistent between the Title Page and the Synopsis

**Approval Date:**

Sponsor Signatory:

|  |  |  |
| --- | --- | --- |
| **[Name]**  **[Title]** |  | **Date** |

Medical Monitor Name and Contact Information [will be provided separately OR can be found in XX]

The investigator signature page is generated internally as a stand-alone document and should be provided to the investigator for signature alongside the final protocol. The investigator should retain the original in the site study files and return a copy to the sponsor for archiving in the trial master file (TMF). In case of a protocol amendment, ensure that the protocol version is noted on the investigator signature page.

Protocol Amendment Summary of Changes Table

**This section may be deleted if this document is not an amendment.**

Protocols should not be developed with the intent to amend; however, if an amendment is required, the following process and template is recommended. Companies should modify this process as appropriate (eg, naming conventions, designation of substantial/nonsubstantial amendment status) to ensure alignment with their internal processes and systems.

**GENERAL INSTRUCTIONS:**

* Protocols should be amended by making the changes directly within the protocol.
* In addition to the summary of changes table, incorporate the changes made as a result of the amendment into the respective CPT sections and create
  + a new clean version
  + a new version with the changes highlighted (ie, tracked changes) to be provided to the health authorities, if required.
* NOTE: For extensive amendments: use the tracked-changes version of the protocol to create a separate document with a tabular listing detailing section changed, initial wording, amended or new wording, reason/justification for change, and reason for substantial amendment as this is now required by many health authorities.
* Include the heading Protocol Amendment Summary of Changes in the table of contents (TOC) as a non-numbered heading.
* Modify the protocol number as appropriate throughout the document as specific to the company (eg, title page, page headers) to designate status as an amendment.
* See Appendix 9, Protocol Amendment History for further instructions and examples for completing this section.
* The common text section titled Document History should be completed for each amendment.
* Amendments should appear in reverse chronological order with the most recent at the top (eg, Amendment 3, 2, 1).
* The Protocol Amendment Summary of Changes table for the current amendment should be maintained directly in front of the TOC.
* The Protocol Amendment Summary of Changes Table(s) for the previous amendment(s) should be moved to Appendix 9, Protocol Amendment History.
* Group changes by rationale and list rationales by order of importance, with the rationale for the most important study design changes listed first. Under each rationale, list changes in order of occurrence in the protocol.

Relevant changes may have been made to the protocol template since the original protocol or last amendment was issued. Check the template change control documentation and discuss with the team to ensure all relevant changes have been added to the protocol and included in the Protocol Amendment Summary of Changes Table.

***NAMING CONVENTIONS*** for differentiation of types of amendments (eg, global, country-specific, site‑specific):

Use International Organization for Standardization (ISO)-Alpha 3 Codes from the United Nations Statistics Department for 3-letter codes to represent country or area name in country-specific amendments: https://www.nationsonline.org/oneworld/countrycodes.htm

Examples can be found in Appendix 9, Protocol Amendment History.

***NUMBERING CONVENTIONS***

* Global amendments should be sequentially numbered (eg, Amendment 1, Amendment 2, Amendment 3, etc).
* Country-specific amendments should list the 3-digit ISO-Alpha 3 Codes (link above) with sequential numbering (eg, for France, the 3-digit code is FRA. The first country-specific amendment for France should be numbered Amendment FRA-1. If a second amendment is required with content specific to France, it would be Amendment FRA-2.).
* When adding an amendment ensure that the country-specific changes are maintained with each global update.
  + A country-specific amendment to a global amendment

or

* + A global amendment to a country-specific amendment.
* For complex trials, the master protocol and the sub-protocol may be amended separately. Therefore, the amendment numbers may not align. The amendment history for the master protocol will be in the master protocol and the amendment history for each sub-protocol will be in the applicable sub-protocol.

Examples can be found in Appendix 9, Protocol Amendment History.

***DOCUMENT HISTORY***

* The Document History table should be inserted at the beginning of each amendment and contain the document number and date for each amendment.
* Global amendments should not list the country- or site-specific amendments in the table.
* Country- and site-specific amendments should list the global amendments.
* Country-specific amendments should not list the site-specific amendments.
* Site-specific amendments should only list country-specific amendments for that specific country.
* If an amendment with identical changes is needed for multiple countries/areas/sites, they may be named as:
  + Region 1 (list country/area codes as ISO-Alpha 3 Codes from the United Nations Statistics Department as noted above)
  + Region 2 (list country/area codes as ISO-Alpha 3 Codes the from United Nations Statistics Department as noted above)
  + Site-specific SS-1 (site numbers)

The rationale for not including the entire list of amendments in the Document History table is that the global amendments apply to all countries and sites, while the country- and site-specific amendments are just that, specific, and therefore do not apply to all.

Examples can be found in Appendix 9, Protocol Amendment History.

List dates of original protocol and all amendments in reverse chronological order.

<Start of common text>

|  |  |
| --- | --- |
| DOCUMENT HISTORY | |
| Document | Date |
| [Amendment X] | [Day-Mon-Year] |
| [Amendment X] | [Day-Mon-Year] |
| [Amendment X] | [Day-Mon-Year] |
| Original Protocol | [Day-Mon-Year] |

Amendment [X] (Day-Month-Year)

<End of common text>

Include the following statement if this amendment will be implemented in any European Union (EU) member state. Include the last phrase for nonsubstantial amendments only.

<Start of common text>

This amendment is considered to be [substantial] [nonsubstantial] based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

<End of common text>

<Start of common text>

Overall Rationale for the Amendment:

The overall rationale (one primary driver) for the changes implemented in the protocol amendment should be provided. In addition, provide a high-level description of the change(s) and a brief scientific rationale for specific items outlined in the table provided (eg, changes to individual inclusion/exclusion criteria). See Appendix 9, Protocol Amendment History for examples of format and green text for sample content.

[INSERT rationale statement]

|  |  |  |
| --- | --- | --- |
| Section # and Name | Description of Change | Brief Rationale |
| [INSERT] | [INSERT] | [INSERT] |
| [INSERT] | [INSERT] | [INSERT] |
| [INSERT] | [INSERT] | [INSERT] |
|  |  |  |
|  |  |  |

<End of common text>

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List of Abbreviations [and Definitions of terms]

* A list of the abbreviations and, if applicable, the definitions of specialized or unusual terms should be provided.
* This list serves as the first appearance of all abbreviations therein. Thus, abbreviations do not need to be spelled out anywhere else in the document text.
* An abbreviation should only be introduced if needed more than once.
* Widely known abbreviations (for example USA, AIDS, common units of measurement) may be used without spelling them out and without adding them to the list.
* Abbreviations used in tables or figures only do not need to be included in this list if already explained in the respective table or figure.
* Each abbreviation is to be used for one term only. Thus, if the same abbreviation is commonly known for more than one term (eg, SD = “standard deviation” or “stable disease”), only one of those terms may be abbreviated in that way; the other terms are either to be spelled out throughout, or are to be represented by alternative, unique abbreviations.
* If a term gets abbreviated, its abbreviation should be used throughout. That is, abbreviations may be used even at the beginning of a sentence.
* The list may be formatted in a space-conscious manner (eg, smaller font size; double-column format)

<Start of example text>

|  |  |
| --- | --- |
| *[abbreviation or term]* | *[definition/explanation]* |
| *[abbreviation or term]* | *[definition/explanation]* |
| *[abbreviation or term]* | *[definition/explanation]* |

<End of example text>

# Protocol Summary

## Synopsis

The protocol synopsis is a short (1 to 2 pages) summary of the key points of the protocol. This section of the protocol should be completed after the main text to ensure consistency with the main text.

The purpose of the protocol synopsis is to provide a concise outline of the key aspects of the study. It may be used for European Union (EU) clinical trial applications (CTAs) and for other external bodies such as institutional review boards [IRBs]/independent ethics committees [IECs]). Its level of detail should not dissuade/discourage the investigator from referring to the main text of the protocol.

**Protocol Title:**

Ensure wording here matches the title page.

**Brief Title:**

Ensure wording here matches the title page.

Regulatory Agency Identifier Number(s):

Include all numbers that are applicable for the study and available at the time of protocol or amendment finalization, eg, investigational new drug (IND) number (include the center number, IND/IDE number, serial number), World Health Organization (WHO) universal trial number, European Clinical Trials Database (EudraCT, EU CT) number, ClinicalTrials.gov. Add type and number as applicable, it should be consistent between the Title Page and the Synopsis

|  |  |
| --- | --- |
| **Registry** | **ID** |
|  |  |
|  |  |

[Pediatric Investigational Plan Number]:

Include pediatric investigational plan and/or pediatric study plan number(s), as applicable. This should be consistent between the Title Page and the Synopsis

Rationale:

The synopsis text should be taken from the main text.

Objectives, Endpoints, and Estimands:

State the primary and secondary objectives and associated endpoints. Be consistent with the main text of the protocol in text and format.

Endpoints and estimands: This should be a high-level description.

|  |  |
| --- | --- |
| Objectives | Endpoints |
| Primary |  |
|  |  |
| Secondary |  |
|  |  |

Overall Design Synopsis:

Be sure the text included in this section is consistent with the text in other sections such as inclusion/exclusion criteria and concomitant medications.

Briefly state:

* Type of design (eg, parallel, crossover, single group) and control method (eg, placebo, active comparator, low dose, historical, or none [uncontrolled]), single or multicenter. Include the kind of control group to be used, if any.
* High-level description of the study population (eg, healthy volunteers, patients with acute lung injury, etc).
* Level and method of blinding (eg, open-label, single-blind, double-blind, double-blind [sponsor unblinded], matching placebo, double-dummy) and the methods to be used to minimize bias on the part of participants, investigators, and analysts.
* High-level description of masking (eg, no, assessor, investigator, caregiver, participant).
* Investigational intervention assignment method (eg, randomization, stratification, both). Do NOT state block size. If assignment to intervention is by randomization, describe when randomization occurs relative to screening.
* Refer to use of an independent data monitoring committee, dose-escalation committee, or similar review group.

<Start of suggested text>

This study design includes [no, assessor, investigator, caregiver, participant] masking.

<End of suggested text>

**Brief Summary:**

Brief Summary is a short description of the clinical study, including a brief statement of the clinical study’s hypothesis. It should be sufficiently detailed to make clear to a lay reader (reading level of 11-13 years) what the study is about and can be used for informed consents and ethics committee submissions as well as the Brief Summary in ClinicalTrials.gov.

Based on NIH expectations and public preferences, the optimal Brief Summary on ClinicalTrials.gov includes the following data elements: condition/disease, study duration, treatment duration, health measurement/observation, and visit frequency.

Additional details:

* Complete sentences
* All abbreviations are defined.
* Formatting includes paragraphs and/or bullets.
* Bibliographic references are avoided, as well as any reference to external documents.
* Limit: 5000 characters

**Health Measurement/Outcome**: What is the primary outcome as given in the objectives being examined to determine the effect from the intervention. This should be included in the protocol title written in lay language, eg, measure the reduction in bad cholesterol; other potential terms: treat, delay, confirm, predict, identify, reduce, correct, reverse, lower, decrease, increase, or improve.

**Study Intervention and Intervention Form:**

Text for this field should be taken from the Intervention table in Section 6.1.

**Condition/Disease**:

The disease, disorder, syndrome, illness, or injury etc. that is being studied included in the protocol title written in lay language. Refer to <https://hso.research.uiowa.edu/medical-terms-lay-language>.

**Study Duration**:

The maximum length of time a participant can be in the study

**Treatment Duration**:

The length of time the intervention will be provided or administered; examples: 3 weeks, 12 months

**Visit Frequency**:

The number of times or how often study visits will take place during the study duration; examples: every 3 weeks, 5 continuous days in the hospital

Complete the suggested text paragraph with values from the list given for each of the indicated fields.

Example:

The purpose of this study is to measure the safety and decrease in agitation with Addiryn tablets compared with placebo tablets in participants with Alzheimer’s dementia. Study details include:

* Study duration: 24 weeks
* Treatment duration: 12 weeks
* Visit frequency: every 3 weeks

<Start of suggested text>

The purpose of this study is to measure [health measurement/observation] with [investigational intervention] [intervention form] [compared with OR in combination with] [investigational intervention] [intervention form] in [participants with [condition/disease]/healthy volunteers].

Study details include:

* The study duration will be up to [numerical value, eg, days, weeks, months].
* The treatment duration will be up to [numerical value, eg, days, weeks, months].
* The visit frequency will be [X].

<End of suggested text>

Number of Participants:

* State the expected number of participants to be screened, enrolled, assigned to investigational intervention, when applicable. For an event-driven study, state the number of events planned along with the number of participants to be assigned to investigational intervention.
* Choose one of the two options listed and modify as appropriate
* Ensure the chosen definition of *enrolled* aligns with other uses of the term throughout the protocol.
* In most complex trials, the eventual total number of participants will not be known at study start. Details for number of participants per intervention cohort should be provided in the applicable sub-protocol.

<Start of suggested text>

Approximately [X] participants will be screened to achieve [X] [enrolled / randomized / assigned to investigational intervention].

OR

A maximum of [X] participants will be [enrolled / randomized / assigned to investigational intervention]

**Note**: *Enrolled* means participants’, or their legally acceptable representatives’, agreement to participate in a clinical study following completion of the informed consent process [and screening]. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. [A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.]

<End of suggested text>

Study Arms and Duration:

Briefly state:

* Total duration of study participation for each participant with sequence and duration of study periods (eg, screening, run-in, fixed dose/titration, follow up/washout periods)
* Dose regimens in each study period and stage (if applicable) including frequency (eg, twice daily) and route of administration and criteria for individualized dosing (eg, participant weight or plasma concentrations), if applicable
* Rules/procedures for any dose changes/adjustments including flexible dosing; dose reductions, interruptions, or tapering; temporary/permanent discontinuation; and any circumstances for resuming study intervention, as applicable

Data Monitoring/Other Committee: [Yes/No]

Use of an independent data monitoring committee, dose-escalation committee, or similar review group.

Also identify additional committee(s) needed for complex trials.

Details for all committees should be included in Appendix 10.1.6 Committees Structure.

<Start of example text>

A [data monitoring committee] has been appointed for this study. The [data monitoring committee (board)] is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

<End of example text>

## Schema

## Schedule of Activities (SoA)

General information:

* Ensure that only essential data are collected. The schedule of activities (SoA) is the primary location for specifying the timing of assessments at each stage of the study. Do not repeat the SoA schedule in the main text.
* Visit windows may be necessary for the data collection. The acceptable windows can be indicated on the SoA by adding ± days or hours/minutes to the visit day or timepoint row.
* If applicable, specify the order of assessments (eg, performing participant-recorded assessments before other assessments to reduce bias or performing electrocardiograms [ECG] or measuring vital signs before blood draws).
* Notes/footnotes (relating to specific procedures) should be minimal, brief, and include key information. If additional details are needed, the notes should refer to the section in the protocol main text where details are provided. Note that Day 0 should not be used as a timepoint.
* Combine assessments on consecutive weeks if they are identical and consider separate tables for separate periods of the study (eg, screening, intervention days, and follow-up). For a multiple-part study, one SoA table for each part of the study is recommended.
* An example of a SoA table is included. Modify as required.
* Protocol language in the SoA section should be kept general and should describe the location of procedures or visits in a non-specific way. In order to facilitate the unanticipated use of a local laboratory/imaging, a home health care nurse, or a participant visit to a family doctor, it is recommended that location information is not specified in the SoA or footnote sections. For instance, specifying the procedure location description in the SoA as “On-site visit” or “On-site laboratory/ imaging”, creates unnecessary protocol deviations if on-site visits cannot be conducted; Study teams are advised to adopt the template language of “Visit” or “Procedure” to ensure intentional flexibility.
* For complex trials, assessments that are specific to a sub-protocol should be outlined in a separate SoA in the applicable sub-protocol. Assessments common to all populations/interventions should remain in the master protocol.

| Procedure | Screening  (up to [X] days before Day 1) | Intervention Period [Days or Weeks, etc] | | | | | | | | | E/D | Follow-up ([X] days after last dose) | Notes  E/D = Early Discontinuation |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| –1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |
| Inclusion and exclusion criteria | X |  |  |  |  |  |  |  |  |  |  |  | [Recheck clinical status before randomization and/or first dose of investigational intervention.] |
| Demography | X |  |  |  |  |  |  |  |  |  |  |  |  |
| Full physical examination including height and weight | X |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history (includes substance use [and family history of premature CV disease]) | X |  |  |  |  |  |  |  |  |  |  |  | Substances: [drugs, alcohol, tobacco, and caffeine] |
| Current medical conditions | X |  |  |  |  |  |  |  |  |  |  |  |  |
| [Highly sensitive serum OR urine] pregnancy test (CBP participants only) | X | X |  |  |  |  |  |  |  |  | X | X | [refer to Section 8.3.5 Pregnancy Testing for instruction on timepoints] |
| [HIV, Hepatitis B and C screening] | X |  |  |  |  |  |  |  |  |  |  |  | Refer to participant libraries for testing required. |
| Laboratory tests (include liver chemistries) | X | X |  |  |  |  | X |  |  | X |  |  |  |
| 12-lead ECG | X |  | X |  | X |  |  |  | X | X |  |  |  |
| Vital signs | X | X | X | X | X | X | X | X | X | X |  |  |  |
| [Randomization] if applicable |  | X |  |  |  |  |  |  |  |  |  |  |  |
| Genetic sample |  |  | X |  |  |  |  |  |  |  |  |  | ICF for genetic sampling should be added per sponsor process (eg, part of ICF or separate ICF). |
| Study intervention |  |  | X |  |  |  |  |  | X |  |  |  |  |
| AE review |  | X | ß=============================à | | | | | | | |  |  |  |
| [Solicited administration-site events if applicable] |  |  | ß=============================à | | | | | | | | X | X | [Pain, redness, or swelling]  Consider separate tables for days with multiple assessments. |
| [Unsolicited AEs if applicable] |  | X | ß=============================à | | | | | | | | X | X | See Appendix 3 for definitions  Consider separate tables for days with multiple assessments |
| SAE review |  | X | ß=============================à | | | | | | | | X | X |  |
| [Device deficiencies if applicable] |  | X | ß=============================à | | | | | | | | X |  |  |
| Concomitant medication review |  | X | ß=============================à | | | | | | | | X | X |  |
| [Study-specific assessments (eg, PK, efficacy)] |  |  |  | | | | | | | |  |  | Consider separate tables for days with multiple assessments |
| PRO assessments (more than one line may be necessary if schedules differ by PRO) |  |  |  | | | | | | | | X |  | Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized. Clarify timing of PRO relative to other study procedures.  Specify plan for collection of PRO measures for participants who discontinue study intervention or discontinue/withdrawal from the study. |

# Introduction

* Overall, this section should be short (recommend 2 to 3 pages) and may be started with an overview description of the investigational intervention, its class, and intended use as well as the study population.
* Consider that the entire protocol will be subject to public disclosure and be succinct.
* As much as possible, reference the investigator’s brochure (IB), investigational directions for use (IDFU), package insert, and other relevant documents; do not duplicate information available elsewhere.
* For complex trials, include a summary of the specifications of the condition, disease, or indication to clearly indicate the eligible participant population in either the master protocol or, for population-specific sub-protocol(s), in the sub-protocol(s). This summary could include, but is not limited to participant age (eg, pediatric, adult), gender, clinical and/or laboratory parameters, prior or concomitant medications, morbidity and comorbidities, and unmet medical need.
* Describe very briefly what is mandated by the master protocol and what can be varied in the intervention-specific or population/disease-specific sub-protocol, if applicable. Describe how the control arm(s), if applicable, will be organized in the master protocol.

<Start of example text>

[XXX] is a novel, potent, and selective long-acting inhaled β2 adrenoreceptor agonist that is being developed for once-daily treatment of asthma and COPD.

<End of example text>

## Study Rationale

* Present a 2- to 3-sentence, coherent, scientific description of the rationale for the study with respect to the purpose of the study. The rationale for the study design appears in Section 4.2.
* Include a brief description of the reasons for doing the study and for doing it at this time. For example, include any key issues for the compound that are being addressed (eg, variable exposure addressed with a new formulation or dosing with food).
* For device studies, include populations and indications for which the investigational device is intended.
* This section should be aligned with the overall development plan for the compound.
* This rationale should be based on the results of previous studies (if relevant) and the characteristics of the disease entity and should be of scientific merit.
* For complex trials, provide the rationale for conducting a complex trial instead of an independent study for each intervention or sub-population.

## Background

This section should be brief (1/2 to 1 page) as the majority of the information is available in existing documents. Include a 1- to 2-sentence description of why the investigational intervention is being developed for the disease (eg, unmet medical need, easier administration, better efficacy expected, better side effect profile). State whether this is a novel class of compounds or a new compound within an established class, and whether this class of compounds has been used before in the therapeutic area. Briefly refer to literature and data relevant to the study.

For studies using an unlicensed investigational intervention: include a very brief summary of key nonclinical/clinical data relevant to the development of the compound and pharmacodynamic/efficacy findings that support development for the indication. Do not duplicate data already summarized in the IB/IDFU/package insert; a reference to the specific IB/IDFU/package insert section is sufficient. When referencing information in the IB/IDFU/package insert or other relevant documents, provide a reference to the section or table where the data are presented.

For studies using marketed compounds or comparators: see the manufacturer’s label (include as a reference in Section 11) or provide a brief description of relevant information. To avoid copyright infringements, do not include a copy of the approved product label in the protocol.

<Start of example text>

Antibiotic resistance has been widely publicized and poses a serious threat to public health worldwide. Research efforts in recent years have become increasingly geared towards discovering and developing new classes of antibiotics with modes of action distinct from those of established agents and activity against resistant strains.

[Investigational intervention name] belongs to a novel structural class of antibiotics: bacterial type II topoisomerase inhibitors (BTIs). The BTIs selectively inhibit bacterial DNA gyrase and topoisomerase IV (homologous type II topoisomerases), which are clinically validated antibacterial targets inhibited by the quinolone family of antibiotics. The BTIs and quinolones bind to a similar region of the same target proteins; however, they recognize distinctly different amino acids. Therefore, they inhibit different stages of the catalytic cycle of the target proteins.

A detailed description of the chemistry, pharmacology, efficacy, and safety of [investigational intervention name] is provided in the [investigator’s brochure/IDFU/package insert].

<End of example text>

## Benefit/Risk Assessment

* Provide a brief assessment of the benefits and risks of study participation. Information should align with the IB, package insert/prescribing information (if applicable), IDFU (for a device product) and investigational medicinal product dossier (IMPD) (if applicable).
* Consider the known and expected benefits and potential risks of the investigational intervention(s), any significant risks associated with study procedures (biopsies, etc) or design (placebo arm, etc), and any measures to control the risks. Cross reference Section 4 Study Design for details of study procedures, dose, and study design justification.
* For an investigational device include risk/benefit analysis from device risk analysis report and details of anticipated serious adverse device effects (SADEs).
* The benefit/risk assessment may include a description of the types of events anticipated in the specific study population (eg, hypoglycemic events are anticipated in a Type 1 diabetes participant, and arrhythmias are anticipated in a participant with Class III/IV heart failure).
* Outcomes of discussions with regulatory authorities as related to benefit/risk and reporting may be summarized here if they provide useful insights for the investigator.
* For studies on drug-device combination (DDC) products, the benefit-risk assessment needs to take into consideration the DDC as a whole (ie, not only the drug).

<Start of example text>

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of [investigational intervention name] may be found in the [investigator’s brochure (IB), participant information leaflet, package insert, development safety update report (DSUR), summary of product characteristics, and/or investigational directions for use (IDFU) for a device product].

<End of example text>

### Risk Assessment

**Investigational Intervention** - Discuss risks related to the investigational intervention(s). Refer to the IB (including section number) for a thorough description of risks related to the intervention generally. Consider the guidance in the DSUR Evaluation of Risks Section 18.1 when taking an inventory of potential risk topics. For the protocol, focus the discussion only on the relevant risks for THIS study. For example, consider the study-specific details that address risks related to investigational intervention (eg, starting dose, dose increments, dose escalation, administration of doses, stopping rules) and the resources required by site(s) (particularly in terms of facilities and staff, procedures, patient population, staff training). Provide a brief description of strategies to mitigate these risks or provide a cross reference to the relevant protocol section (eg, inclusion/exclusion criteria, participant monitoring, withdrawal criteria, dose selection, comparison to nonclinical no effect levels, duration of dosing).

**Study Procedures** - Consider risks associated with the study design and procedures specific to THIS study (eg, biopsies) or design (eg, placebo arm), and any measures to control the risks. This is not intended to be an exhaustive list of all possible risks associated with study procedures but should focus on the unique risks inherent in the design or less common or high-risk procedures. Cross reference Section 4 Study Design for details of study procedures, dose, and study design justification. Provide a brief description of strategies to mitigate these risks or provide a cross reference to the relevant protocol section (eg, inclusion/exclusion criteria, participant monitoring, withdrawal criteria, dose selection, comparison to nonclinical no effect levels, duration of dosing).

**Other** - Consider risks associated with other study interventions (eg, comparators, challenge agents, imaging agents, medical devices). Insert a line for each, as needed.

### Benefit Assessment

The benefit assessment should be written from the perspective of an individual participant. This section should describe any physical, psychological, social, legal or any other benefits (immediate and/or long-term) to an individual participant as a result of participating in the study.

Benefits to society in general may also be included but should be discussed separately.

Benefit considerations may include:

* Potential benefit of receiving investigational intervention during study duration that may have clinical utility (if applicable)
* Contributing to the process of developing new therapies in an area of unmet need – this may be particularly relevant for Clinical Pharmacology studies
* Provision of nondrug therapy (eg, compression stockings) if applicable
* Medical evaluations/assessments associated with study procedures (eg, physical exam, ECG, labs, etc)

Guidelines regarding payment to participants vary by region and country. Because payments cannot be considered a benefit, do not include discussion of payment (whether as an inducement to participate or as compensation for time and inconvenience to participants) in this analysis. For this assessment, provision of incidental care should also not be considered a benefit.

### Overall Benefit Risk Conclusion

Provide a succinct concluding statement on the perceived balance between risks that have been identified from cumulative safety data, protocol procedures and anticipated efficacy/benefits within the context of the proposed study. Risks need to be weighed against the benefits for the **individual participant.**

Clinical studies should generally pose only minimal risks to incapacitated participants, minors, pregnant or breastfeeding women, and clinical studies conducted in emergency situations. Refer to local guidelines for specific requirements or benefit/risk thresholds in these populations and ensure that these are addressed here, if applicable.

Outcomes of discussions with regulatory authorities as related to benefit/risk and reporting may be summarized here if it provides useful insights for the investigator.

<Start of example text>

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with [investigational intervention] are justified by the anticipated benefits that may be afforded to participants with [indication].

<End of example text>

# Objectives, Endpoints, and Estimands

The protocol is the primary source of information for protocol endpoint registration on public registers (eg, ClinicalTrials.gov).

*Objectives*:

* Objectives and endpoints for specific therapeutic areas may be accessed in the therapeutic area libraries. List each scientific objective of the study, clearly and concisely, differentiating between primary, secondary, and tertiary (or other/exploratory) objectives. The objectives should present the questions that the study is designed to answer (which can include predefined safety parameters). Secondary objectives should not merely reiterate the secondary endpoints of the study.
* State specific PRO objectives. Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal timepoint or period of interest.
* The objectives should be stated with sufficient specificity that the reader can easily understand the intended context (eg, Superiority of [intervention X] vs control when the intervention is taken as directed). Consultation or review by a statistician is recommended.

*Endpoints:*

* An endpoint is defined in draft ICH E8(R1) as a “subject-level attribute of interest”, so ensure wordings like “proportion of participants reaching [target]” are not used, but rather “Participant reaching [target] (yes/no)” when defining endpoints.
* Ensure that there is an endpoint with associated timepoint or timeframe for each study objective including exploratory objectives, if applicable, and that there are no endpoints without a corresponding objective.
* Be specific and selective when choosing and describing primary and secondary endpoints because results for all primary and secondary endpoints are required to be listed on the ClinicalTrials.gov website and other public registers.
* In a study designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or be a surrogate or other endpoint with a demonstrated ability to predict clinical benefit.
* Avoid vague descriptions of primary and secondary endpoints that encapsulate a large number of measures and timepoints, such as “safety and tolerability as determined by AE reporting, laboratory values, vital signs, and ECGs.” In a typical clinical study this could equate to hundreds of endpoints, all of which must be registered on ClinicalTrials.gov and other public registers. Consider including such general objectives and endpoints in the Tertiary/Exploratory/Other section, which will not be registered on public registers.
* If there is a safety measure of special relevance, this can be included as a specific primary or secondary endpoint (eg, a specific lab measurement or an adverse event of special interest).
* It is recommended not to include study procedures as an endpoint; only the data resulting from the procedure should be an endpoint. For example, abnormal physical examination should not be designated as an endpoint unless it is clear where this endpoint is captured and how it will be summarized in the clinical study report. Details of procedures should be placed in Section 8 Study Assessments and Procedures. Consider whether the desired endpoints will be achievable in case of unexpected findings, technical/equipment issues, or personnel failure.
* If a clinical outcome assessment (COA) is included in the study, mention the concept being measured (eg, fatigue) as well as the instrument (eg, fatigue as measured by the fatigue scale in the Functional Assessment of Cancer Therapy-Anemia [FACT-An]). Avoid the term quality of life and use a more specific term such as physical functioning or vitality.
* If additional tertiary/exploratory/other endpoints (eg, pharmacodynamic endpoints) may be explored, consider addition of a general statement giving an indication of the types of endpoints that might be explored. For example, in cardiovascular studies, a statement such as “Additional atherosclerotic biomarkers may be explored” may be appropriate. The study procedures section of the protocol should clarify, to the extent possible, how and when the additional endpoints will be selected, the types of endpoints that may be assayed (eg, protein, messenger ribonucleic acid), whether existing or additional samples would be used for these assays, and how any changes to exploratory endpoints will be documented.
* Identify surrogate markers if used as study endpoints.

*Estimands:*

* It is recommended that objectives and endpoints be presented together in a table (see example) to ensure all endpoints are aligned with an objective. Further, it is recommended to include the definition(s) of the estimands below the table.
* Estimands include 5 attributes: the treatment condition of interest, the population, variable (or endpoint), details of how to account for intercurrent events (ICEs), and the population-level summary for the variable.
* The ICH E9(R1) addendum tries to distinguish the development of the estimand, ie, the treatment effect of interest, and the conduct of a study for estimation. While in practice the estimand is defined in order to plan a study, ideally it should be possible to communicate the estimand without reference to study specific context. For example, the population should reflect the set of patients or individuals targeted by the clinical question, represented by the study population. Describing the population, the appropriate term “patients” or “individuals” should be used instead of referring to study participants. The same is true for the treatment conditions: the test intervention and the control to which comparison(s) will be made should be mentioned, giving the name of the specific intervention, but not simply referring to “study” intervention.
* The estimands should be clear and include sufficient detail on each attribute.
* Estimands are mandatory for confirmatory studies (ie, studies in which pre-specified hypotheses are evaluated, see ICH E9), but it is also strongly recommended to include estimands in other types of studies.
* Define one or more estimands for the primary and key secondary objectives. An estimand description is not required for tertiary/exploratory objectives.
* Include the clinical question(s) of interest that drives the estimand(s) and provide a rationale for the chosen estimand(s), eg, per regulatory guidance or per clinical justification such as estimating the treatment effect without the confounding effect of rescue intervention or the treatment effect including the effect of rescue medication to reflect clinical practice. Make sure to address all ICEs and all other attributes of the estimand and justify accordingly.
* If including more than one estimand for the primary objective, one of them should be named primary.
* If for a particular study different primary estimands/endpoints are required for different regulatory authorities, it should be specified which one is considered primary for each regulatory authority.
* Indicate not applicable or remove the section if no estimand is defined for the study.

For complex trials, the master protocol should have an overarching scientific hypothesis and the primary objective should not be changed during the conduct of the trial.

<Start of suggested text>

|  |  |
| --- | --- |
| Objectives | Endpoints |
| Primary |  |
|  |  |
| Secondary |  |
|  |  |
| [Tertiary/Exploratory/Other] |  |
|  |  |

<End of suggested text>

Estimand(s) for Primary Objective(s)

**[Primary estimand / coprimary estimands / Multiple primary estimands]**

<Start of example text>

The primary clinical question of interest is:

What is the [population-level summary] in [endpoint] in [patients with [condition/disease]/individuals] treated with intervention X vs. intervention Y regardless of discontinuation of investigational intervention for any reason and regardless of initiation of rescue medication or change in background medication (dose and product)?

The estimand is described by the following attributes:

* Population:

[patients with [condition/disease]/individuals]

* Endpoint:

change from baseline to [timepoint] in [health measurement/outcome]

* Treatment condition:

the investigational interventions regardless of discontinuation for any reason, with or without rescue medication or change in background medication (treatment policy strategy).

* Remaining intercurrent events:

The intercurrent events “intervention discontinuation for any reason” and “initiation of rescue medication or change in background medication (dose and product)” are addressed by the treatment condition of interest attribute. There are no remaining intercurrent events anticipated at this time.

* Population-level summary:

difference in mean changes between treatment conditions

Rationale for estimand: [rationale].

<End of example text>

Supplementary Estimand(s)

Estimands for Secondary Objective(s)

Secondary and supplementary estimands should be defined for each secondary objective as relevant.

**Secondary estimand(s) for Secondary Objective [label]**

<Start of example text>

The clinical question of interest is for the secondary objective [label]:

What is the difference in the proportion of [patients with [condition/disease]/individuals] achieving [response criterion] where discontinuation of investigational intervention for any reason is considered to be a failure (non-response) treated with intervention X vs. intervention Y regardless of initiation of any additional rescue intervention, such as [medication/surgery/behavioral]?

The estimand is described by the following attributes:

* Population:

Patients with [condition/disease]

* Endpoint:

Achievement of [rescue criterion], where discontinuation of investigational intervention for any reason is considered to be a failure (composite strategy)

* Treatment condition:

The investigational interventions with or without any other any additional rescue intervention, such as [medication/surgery/behavioral] (treatment policy strategy)

* Remaining intercurrent events:

The intercurrent event “discontinuation of investigational intervention for any reason” is addressed by the endpoint attribute using the composite strategy. The intercurrent event “any additional rescue intervention, such as [medication/surgery/behavioral] is addressed by the treatment condition attribute using the treatment policy a strategy. There are no remaining intercurrent events anticipated at this time

* Population-level summary:

Difference in proportion of patients with response

Rationale for estimand: [rationale]

<End of example text>

Supplementary Estimand(s)

Estimands for [Tertiary/Exploratory/Other] Objectives

Tertiary/Exploratory/Other and supplementary estimands should be defined for each Tertiary/Exploratory/Other objective as relevant.

[Tertiary/Exploratory/Other] Estimand(s) [label]

Supplementary Estimand(s)

# Study Design

## Overall Design

* Do not include study schema.
* Do not include the SoA here.
* Use bullets rather than lengthy text, if possible.
* For studies with estimand(s), ensure the design is aligned to the estimand(s) defined in Section 3
* Include a brief summary of the study design (eg, parallel, crossover, single group) and control method (eg, placebo, active comparator, low dose, historical, or none [uncontrolled]), single or multicenter. Include the kind of control group to be used, if any.
* Include a high-level description of the study population (eg, healthy volunteers, patients with acute lung injury).
* Level and method of blinding (eg, open-label, single-blind, double-blind, double-blind [sponsor unblinded], matching placebo, double-dummy), and further methods to be used to minimize bias on the part of participants, investigators, and analysts.
* Study intervention assignment method (eg, randomization, stratification, both). Do NOT state block size. If assignment to intervention is by randomization, describe when randomization occurs relative to screening. Do not put sample size justification here. This is covered in Section 9 Statistical Considerations.
* Refer to any use of an independent data monitoring committee, dose-escalation committee, or similar review group and cross-reference Appendix 10.1.6 Committees Structure.
* Total duration of study participation for each participant with sequence and duration of study periods (eg, screening, run-in, fixed dose/titration, follow up/washout periods)
* Describe any provisions for extending the study or entry to rollover studies (cross-reference Section 6.7 Continued Access to Study Intervention after the End of the Study). Do not duplicate information.
* Include any plans to obtain long-term follow-up information regarding the participant’s safety or survival status as noted in the ICF and assent form.
* For studies including participants of childbearing potential, include plans for collection of follow up information on maternal and fetal safety should they become pregnant during the trial. If applicable, include cross-reference to Section 8.4.5. In addition, refer to Section 10.8 for local follow-up requirements, as referenced in the TransCelerate Interpretation of Pharmacovigilance Guidances & regulations Pregnancy and Breastfeeding Landscape Assessment.
* See therapeutic area libraries for additional guidance for studies in specific therapeutic areas.
* A protocol deviation is related to a data point or process identified in the protocol or documents referenced in the protocol (eg, laboratory manual). When designing the study, limit items that may generate deviations whenever possible. Reduce the number of reference documents to those essential for the conduct of the study.

## Scientific Rationale for Study Design

* Provide scientific rationale for any features of the study design and chosen control. Include any key ethical issues. Do not reiterate the details provided in the IB/IDFU or other documents.
* State if design is well established or best practice including a justification for use of placebo control; adherence to regulatory convention is usually not sufficient justification.
* Describe why the primary endpoint is clinically relevant and how it provides a reliable and valid measurement of the intended intervention effect.
* Discuss how the primary endpoint measures direct benefit in how the participant feels, functions, or survives and what would constitute a clinically meaningful effect.
* If a measure of direct benefit is not proposed, describe how a proposed surrogate endpoint substitutes for how a participant feels, functions, or survives, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict benefit.
* If applicable, provide a scientific rationale that including a vulnerable study population (eg, pediatric participants or participants requiring emergency care) has the potential to produce a clinically relevant benefit.
* Provide justification for the sex and age allocation of participants and if a specific sex or age group is excluded from or underrepresented in the study, an explanation of the reasons and justification for these exclusion criteria.
* If applicable, describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.
* If an auxiliary medicinal product (AxMP) or noninvestigational medicinal product (NIMP)/diagnostic agent to be used in the study is a marketed compound but is not used as per the approved label, a justification needs to be added in the protocol for the intervention to still be classified as an AxMP/NIMP.
* For complex study designs:
  + Provide justification for why conducting a complex study is appropriate in the specific disease area.
  + What are the advantages and efficiencies gained with such a design compared to a traditional study design evaluating a single intervention? Explain the potential rationale for effective interventions and how many interventions could be evaluated as part of the complex study. Is there a maximum number of interventions (overall/at any point of time) that can be evaluated?
  + Explain what the current standard care/control arm, if applicable, is at present and under what conditions the control arm could change during the study.

### Patient Input into Design

Describe any patient involvement in the design of the clinical study and any patient suggestions implemented.

<Start of example text>

4.2.1.1 Obtaining Study Participant Feedback (Voluntary):**​**

This trial will include an option for patients to complete a questionnaire, the ‘Study Participant Feedback Questionnaire’, which will give participants the opportunity to provide feedback on their clinical trial experience. Participants may be asked to complete a survey, at one or more timepoints, to collect feedback on their experience with participation in the clinical trial. Individual participant level responses will be anonymous to the investigator and site staff and so will not be reviewed by investigators. Coded responses would be used by the sponsor to understand where improvements can be made in the clinical trial process. We may combine responses across studies and with data collected as part of the study, such as demographics, to investigate correlations with the participant experience. We may share aggregated data, maintaining individuals’ anonymity, with site staff so they can take steps to understand and improve the participant experience at their site. This questionnaire does not collect data about the participant’s disease, symptoms, treatment effect or adverse events and therefore would not be trial data. Consequently, this data does not contribute to any endpoints on the study and will be analyzed and reported separately from the clinical study data. The results of this participant experience analysis may be published or presented at scientific meetings, with the Sponsor complying with the requirements for publication. Should any spontaneous information be collected about AEs, this would be reported and transferred to the safety database.

<End of example text>

## Justification for Dose

Provide justification for the selection of the doses of all study interventions. Cross-reference Section 6.6 Dose Modification as needed.

For a device product, state the rationale for the proposed route of administration (eg, injection plane or technique, method of implantation) for each study intervention and provide justification for its selection. Consider adding the suggested text for device products.

For first-time in human (FTiH) studies, the scientific rationale for the starting dose should be briefly described.

If the study design foresees dose escalation, describe the maximum allowed increase from one subset to the next and mention on which data it is based (eg, nonclinical studies)

<Start of example text>

For this device, the term dose refers to [insert as appropriate].

<End of example text>

<Start of example text that can be used with study designs that incorporate dose adjustment decisions>

This protocol allows some alteration from the currently outlined dosing schedule, but the [maximum daily dose and/or (predicted) maximum/cumulative exposure] will not exceed [X].

OR

The decision to proceed to the next dose level of [X] (either an increase or a decrease) will be made by the study team [and the investigator] based on safety, tolerability, and preliminary [PK and/or pharmacodynamic] data obtained in at least [X] participants at the prior dose level.

OR

The dosing schedule may be adjusted to expand a dosing cohort to further evaluate [safety, PK, and/or pharmacodynamic] findings at a given dose level or to add cohorts to evaluate [up to X] additional dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as those described for other study participants/cohorts.

OR

Dose escalation will be temporarily halted and no further participants will be dosed until completion of a full safety review if:

* Moderate or severe AEs are consistently observed across participants in a cohort.
* Unacceptable pharmacological effects that are reasonably attributable to [study intervention] in the opinion of the investigator are observed in more than [X]% of the participants in a cohort.

Relevant reporting and discussion with the medical monitor, relevant [X] personnel, and the IRB/IEC will take place before resumption of dosing.

OR

If the same SAE occurs in more than [X] participants in a cohort, then dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the medical monitor, relevant [X] personnel, and the IRB/IEC will take place before resumption of dosing.

The above criteria will apply even if measured PK parameters are below the prespecified PK stopping criteria, and every effort will be made to take a blood sample at the time of the AE for PK analysis.

<End of example text that can be used with study designs that incorporate dose adjustment decisions>

## End-of-Study Definition

Distinguish between the end of the study (EU definition) and study completion (US CT Registry definition: final date on which data were or are expected to be collected) if they are not the same.

For complex trials: Distinguish between participant completion, intervention cohort completion, and complex trial completion, as applicable.

<Start of common text>

The end of the study is defined as the date of [the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study globally].

A participant is considered to have completed the study if the participant has completed all periods of the study including [the last visit] or [the last scheduled procedure shown in the SoA].

<End of common text>

# Study Population

Criteria should be numbered according to company process.

* A selection criterion should be phrased as either inclusion or exclusion criterion (whatever is more appropriate), but not as both in- and exclusion criterion.
* As applicable, criteria for temporarily delaying enrollment, assignment to or administration of study intervention may be added to appropriate section(s).
* For complex trial designs, any inclusion/exclusion criteria provided in the master protocol apply to all sub-protocols. Definition of master protocol inclusion/exclusion criteria should be carefully evaluated to avoid amendments to address needs for subsequent sub-protocols.

<Start of common text>

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

<End of common text>

## Inclusion Criteria

General Points:

* List the criteria necessary for participation in the study. Ensure that each criterion can be easily assessed on the basis of measurable data and answered with yes/no responses.
* When choosing inclusion criteria, consider that study participants should be representative of the patient population to which the results will be generalized.
* The choice of the study population in a Phase 2 or Phase 3 clinical study should reflect the intended use of the intervention. This is particularly relevant for planning multiregional studies and for the range of subgroups that may be relevant to evaluate.
* If measures to enrich the study population for prespecified subgroups of interest are used, they should be described here.
* In general, laboratory results required for eligibility should be listed as inclusion criteria rather than exclusion criteria.
* The use of double negatives should be avoided (eg, no indication of prior noncompliance with the intervention regimen).
* As applicable, the inclusion criteria should take into consideration the medical device component for DDC products and the usability aspects for the targeted population.
* Specify any PRO-specific eligibility criteria (eg, language/reading requirements or pre‑randomization completion of PRO). If PROs will not be collected in the entire study sample, provide a rationale and describe the recruitment method for obtaining the PRO subsample.

Participants are eligible to be included in the study only if all of the following criteria apply:

|  |
| --- |
| Age |
| <Start of suggested text>   1. Participant must be [18] [or the legal age of consent in the jurisdiction in which the study is taking place] to [X] years of age inclusive, at the time of signing the informed consent.   <End of suggested text> |
| Type of Participant and Disease Characteristics |
| For studies in healthy volunteers, begin with this criterion.  <Start of suggested text>   1. Participants who are overtly healthy as determined by medical evaluation including [medical history, physical examination, laboratory tests, and cardiac monitoring].   OR   1. Participants who are [insert criteria]  * For studies in patients, provide disease‑related considerations: standard, accepted diagnostic criteria (consider supplying laboratory reference ranges or clinical diagnostic criteria in an appendix). Include duration/severity of disease or disorder if appropriate. * When appropriate, specify a realistic and pragmatic inclusion range for each test or marker of interest. Take into consideration any known assay variance or error rate as well as biological variation to avoid creating protocol violation issues. * For details on rescreening, insert a cross-reference to Section 5.4, if appropriate. * Check whether additional information associated with the disease area can be found in the therapeutic area libraries.   <End of suggested text> |
| Weight |
| Consider whether any restriction on weight or BMI is needed for this study intervention/stage of development and delete if not required.  <Start of suggested text>   1. Body weight within [insert range including units] and BMI within the range [X – X] kg/m2 (inclusive)   <End of suggested text> |
| Sex and Contraceptive/Barrier Requirements |
| All references to male & female pertain to sex assigned at birth, most often based on the infant’s physical characteristics.   1. [male and/or female] assigned at birth, inclusive of all gender identities.   If there are no contraceptive requirements in the study, remove the statement “Contraceptive use by participant and participant partners …”. Modify as appropriate based upon participant inclusion.  <Start of common text>  Contraceptive use by [participants or participant partners] should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.  Male participants:  See participant libraries for common text to include here.  Female participants:  See participant libraries for common text to include here.  <End of common text> |
| Informed Consent |
| <Start of common text>   1. Signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.   <End of common text> |
| Other Inclusion Criteria |
| 1. Enter Other Inclusion Criteria |

## Exclusion Criteria

Exclusion criteria: See participant and therapeutic area libraries for suggested text. Numbering will start again for exclusion criteria or be continued from the inclusion criteria dependent on company practice or requirements of technology solutions.

Participants are excluded from the study if any of the following criteria apply:

|  |
| --- |
| **Medical Conditions** |
| 1. [ ] |
| **LiverSafety** |
| 1. [ ] |
| **Prior/Concomitant Therapy** |
| 1. [ ] |
| **Prior/Concurrent Clinical Study Experience** |
| 1. [ ] |
| **Diagnostic Assessments** |
| 1. [ ] |
| **Other Exclusion Criteria** |
| 1. [ ] |

## Lifestyle Considerations

If this section is not applicable, include a statement that no restrictions are required. Do not omit section.

If applicable, describe any of the lifestyle considerations (diet, smoking habits, alcohol, or recreational drug consumption, etc) that could be of relevance for the study and any restrictions during any of the study periods. For example, include a statement about exposure to sunlight for study interventions with photosensitivity potential.

Level 3 headings may not be applicable for all studies (eg, vaccines).

* [ ]
* [ ]

### Meals and Dietary Restrictions

* Food and drink restrictions before the start of pharmacokinetic (PK) sample collections
* Timing of meals relative to dosing
* Ensure consistency in this section with other parts of the protocol and cross-reference other sections (eg, exclusion criteria) as needed.
* If the exact timing of meals is listed in the SoA, do not repeat this information here. Instead, include a reference to the SoA.

<Start of example text>

* Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] from [X days] before the start of study intervention until after the final dose.
* For food effect studies, water restrictions may be needed. No water is allowed until 2 hours after dosing, after which time water is allowed ad libitum.

<End of example text>

### Caffeine, Alcohol, and Tobacco

* Restrictions are dependent on the known metabolism of the study intervention to eliminate any potential for PK interactions and possible effects of caffeine- and xanthine-containing products on ECG results or other pharmacodynamic endpoints (eg, blood pressure).
* The possible effects of alcohol on PK, pharmacodynamic interactions, or laboratory parameters, such as liver function tests, should also be addressed by restrictions in this section.

<Start of example text>

* During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for [X hours] before the start of dosing until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
* During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
* Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit. [OR] Use of tobacco products will not be allowed from [screening/the start of dosing] until after the final follow-up visit.

<End of example text>

### Activity

Study-specific restrictions may apply depending on the nature and frequency of assessments; eg, in FTiH, activity may be further restricted by ensuring participants remain in bed for 4 to 6 hours after dosing, or for studies with interventions known to cause photosensitivity, activities such as sunbeds may be restricted.

<Start of example text>

1. Participants will abstain from strenuous exercise for [X hours] before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

<End of example text>

### Other Restrictions

Additional study-specific restrictions may apply that do not fit in the previous categories; eg, participants may be asked to refrain from donating blood for the duration of their study participation.

## Screen Failures

State whether rescreening is permitted. Individual inclusion/exclusion criteria may also state whether a repeat procedure is allowed without being considered a rescreen.

If rescreening is permitted, the following points should be addressed:

* State how many times/how often rescreening is allowed.
* State the time period for repeating procedures/rescreening.
* State the entry criteria/parameters that can be reassessed for individuals who previously failed screening,
* State whether a new informed consent is required for each re-screening.
* State whether a new participant number is issued for each re-screening

<Start of common text>

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently [assigned to study intervention/entered in the study]. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

<End of common text>

<Start of common text>

Individuals who do not meet the criteria for participation in this study (screen failure) [may/may not] be rescreened. [Rescreened participants should be assigned a new participant number for every screening/rescreening event.]

<End of common text>

## Criteria for Temporarily Delaying [Enrollment/Randomization/Administration of Study Intervention]

Insert suggested text from participant or therapeutic libraries if relevant.

# Study Intervention(s) and Concomitant Therapy

* Ensure study interventions and allowed or forbidden additional interventions are aligned with the treatment condition attribute of the defined estimand(s), if applicable.
* Ensure that sufficiently detailed information for concomitant, background and rescue interventions is collected to ensure that the estimand(s) can be estimated. For example, type, dose (if a medicinal product), dates and durations. Consider if this information also needs to be collected after discontinuation of investigational intervention.

<Start of common text>

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

<End of common text>

## Study Intervention(s) Administered

* It is preferred that interventions are described in a table and that text be minimized.
* The precise interventions or diagnostic agents to be administered in each arm of the study and for each period of the study should be described including route and mode of administration, dose, and dosage regimen and duration of intervention.
* Include information for all study interventions (eg, placebo, comparators, background medication, rescue medication). If any interventions or diagnostic agents will be provided by the sponsor, consider adding details.
* All interventions must be designated as an investigational medicinal product (IMP) or NIMP/AxMP. If uncertain as to whether an intervention is an IMP or an NIMP/AxMP, refer to definitions provided below or to current EU guidance on IMP and NIMP/AxMP.
  + An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. Medicinal products with a marketing authorization are IMPs when they are to be used as the test substance, reference substance, or comparator in a clinical study, provided the requirement(s) in the definition is/are met.
  + An NIMP/AxMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, eg, concomitant or rescue/escape medication used for preventative, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.
* For devices, include details on the setup and use of the device (see Section 6.1.1 Medical Devices). A device user manual can be included as an appendix.

**The tables should be modified as needed. Instructions for the tables are as follows:**

Table 1:

* Intervention Label: Unique identifier to represent the intervention and its related characteristics. It will be used to populate the Associated Intervention Labels cell in the Arms table.
* Intervention Name: Enter a generic (INN) or trade name, if required as per CMC, if applicable.
* Intervention Description: Include details that can be made public about the intervention, sufficient to distinguish the intervention from other similar interventions studied in the same or another clinical study. For example, interventions involving drugs may include dosage form, dosage, frequency, and duration. Limit: 1000 characters.
* Type: Select one option from this list:
  + Drug: Including placebo
  + Device: Including sham
  + Biological/Vaccine
  + Procedure/Surgery
  + Radiation
  + Behavioral: For example, psychotherapy, lifestyle counseling
  + Genetic: Including gene transfer, stem cell and recombinant DNA
  + Dietary Supplement: For example, vitamins, minerals
  + Combination Product: Combining a drug and device; a biological product and device; a drug and biological product; or a drug, biological product, and device
  + Diagnostic Test: For example, imaging, in vitro
  + Other: Edit as appropriate.
* Dose Formulation: Select one option from the list:
  + Tablet
  + Ampule
  + Capsule
  + Other: Edit as appropriate.

For device protocols, include device configuration/style/models.

* Unit Dose Strength(s): Include dose strength information
* Dosage Level(s): Include dose amount and frequency
* Route of Administration: Select one option from the list:
  + Oral
  + IM
  + IV infusion
  + IV injection
  + Other: Edit as appropriate.
* Use: Select one of the following:
  + Experimental
  + Placebo Comparator
  + Active Comparator
  + Sham Comparator
  + Rescue Medication
  + Background Intervention
  + Challenge Agent
  + Diagnostic
  + Other.
* Definition of IMP and NIMP/AxMP is based on guidance issued by the European Commission. Regional and/or country differences in the definition of IMP/NIMP/AxMP may exist. In these circumstances, local legislation is followed.
* Sourcing: Include sourcing-related information, eg, centrally by sponsor or locally by the study site, subsidiary, or designee.

For device protocols, include manufacturer.

* Packaging and Labeling: Include information on how the study intervention will be packaged and labeled.
* Current/Former Names(s) or Alias(es): If applicable, add current and former name(s) or alias(es), if any, different from the intervention name(s) that the sponsor has used publicly to identify the intervention(s), including, but not limited to, past or present names such as brand name(s) or serial number(s).

<Start of suggested text>

Table 1. Study Intervention(s) Administered

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention Label** |  |  |  |  |
| **Intervention Name** | [Generic (or trade name if required) as per CMC, if applicable, or sponsor number] | [Generic (or trade name if required) as per CMC, if applicable, or sponsor number] | [Placebo] | [Any additional products provided as part of the study including rescue medications or challenge agent] |
| **Intervention Description** | [eg, dosage form, dosage, frequency] | [eg, dosage form, dosage, frequency] | [eg, dosage form, dosage, frequency] | [eg, dosage form, dosage, frequency] |
| **Type** | [drug/device/biologic] | [drug/device/biologic] | [drug/device/biologic] | [drug/device/biologic] |
| **Dose Formulation** | [tablet/ampule/capsule] | [tablet/ampule/capsule] | [tablet/ampule/capsule] | [tablet/ampule/capsule] |
| **Unit Dose Strength(s)** | [dose strength of the product ie, each unit] | [dose strength of the product ie, each unit] | [dose strength of the product ie, each unit] | [dose strength of the product ie, each unit] |
| **Dosage Level(s)** | [dose amount and frequency] | [dose amount and frequency] | [dose amount and frequency] | [dose amount and frequency] |
| **Route of Administration** | [oral/IM/IV infusion/IV injection] | [oral/IM/IV infusion/IV injection] | [oral/IM/IV infusion/IV injection] | [oral/IM/IV infusion/IV injection] |
| **Use** | [experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other] | [experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other] | [experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other] | [experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other] |
| **IMP and NIMP/AxMP.** | IMP or NIMP | IMP or NIMP | IMP or NIMP | IMP or NIMP |
| **Sourcing** | [Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer] | [Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer] | [Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer] | [Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer] |
| **Packaging and Labeling** | Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement. | Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement. | Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement. | Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement. |
| **[Current/ Former Name(s) or Alias(es)]** | Current/former name(s) or alias(es) | Current/former name(s) or alias(es) | Current/former name(s) or alias(es) | Current/former name(s) or alias(es) |

Table 2:

* Arm Title: Please enter 1 arm name per column (this name should be used consistently across all related documents).
* Arm Type: Role of each arm in the clinical study. Select one option from this list:
  + Experimental
  + Placebo Comparator
  + Active Comparator
  + Sham Comparator
  + No Intervention
  + Other
* Arm Description: If needed, additional descriptive information (including which interventions are administered in each arm) can be added to differentiate each arm from other arms in the clinical study. Limit: 1000 characters. Delete row if not required
* Associated Intervention Labels: List all the interventions to be administered in each arm exactly as listed in the first table.

Table 2. Study Arm(s)

|  |  |  |  |
| --- | --- | --- | --- |
| **Arm Title** | Enter Arm name | Enter Arm name | Enter Arm name |
| **Arm Type** | [experimental, placebo, active comparator, sham comparator, no intervention, or other] | [experimental, placebo, active comparator, sham comparator, no intervention, or other] | [experimental, placebo, active comparator, sham comparator, no intervention, or other] |
| **[Arm Description]** | [eg, Participants will receive [X] 20 mg BID on Day 1 of each 21-day cycle. [Z] will be administered on Day 1 for 4 cycles.] | [eg, Participants will receive [X] 20 mg BID on Day 1 of each 21-day cycle. [Z] will be administered on Day 1 for 4 cycles.] | [eg, Participants will receive [X] 20 mg BID on Day 1 of each 21-day cycle. [Z] will be administered on Day 1 for 4 cycles.] |
| **Associated Intervention Labels** |  |  |  |

<End of suggested text>

### Rescue Medicine

If rescue therapy is permitted, consider using the suggested text provided.

The efficacy section should address when endpoints (eg, pain scores) are to be assessed with respect to dosing of rescue medication if relevant.

Note that intake of rescue medication may affect the estimand (intercurrent event as one of the estimand attributes).

<Start of example text>

The study site [will/will not] supply [specify type] rescue medication that will be [provided by the sponsor/obtained locally]. The following rescue medications may be used:

* [X]
* [X]

Although the use of rescue medications is allowable [at any time during the study], the use of rescue medications should be delayed, if possible, for at least [insert timeframe] following the administration of study intervention. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

<End of example text>

### Medical Devices

* This section is required for medical devices and can be deleted for non-device protocols. A device user manual can be included as an appendix to the protocol.
* Describe any sponsor-provided medical device(s) including any materials that will be in contact with tissues or body fluids. Include details of any medicinal products, human or animal tissues or their derivatives, or other biologically active substances.
* **Consult with Regulatory Affairs of sponsor** if use of a device is required for the study because not all devices are defined as medical devices and different regions have different definitions for a medical device.
* Examples of sponsor medical devices include, but are not limited to, the following: metered dose inhaler, autoinjector, inhalation spacers, measuring cups, measuring spoons, pediatric oral syringes, and dry-powder inhalers.
* For devices, if a control product is used, ensure that description of its use is consistent with the applicable DFU in countries where the study will be conducted.
* Specifically note whether the device is cleared by the FDA or not. If any diagnostic tests have not been approved or cleared for the indications the protocol is designed to investigate, a detailed test protocol (including specimen collection/storage/processing/testing procedures, result interpretation guide, the number and name(s) of US and non-US testing sites) and a summary/report of test validation studies should accompany the protocol submission.
* The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.

<Start of example text>

1. The [sponsor] manufactured medical devices (or devices manufactured for [sponsor] by a third party) provided for use in this study are [list here].
2. Other medical devices (not manufactured by or for [sponsor]) provided for use in this study are [list here].
3. Instructions for medical device use are provided [cross reference the location of such information].
4. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

<End of example text>

## Preparation, Handling, Storage, and Accountability

Instructions for the preparation of study interventions, including assembly of devices, should be provided (eg, reconstitution, mixing). If the instructions are lengthy or complicated, it is acceptable to reference the label (if applicable) or include them as an appendix to the protocol or as a separate document(s) provided to the site (eg, pharmacy manual). If provided to the site as a separate document(s), this should be noted in this section.

For device protocols:

* List key study materials other than the study intervention that will be necessary at the site. Any critical special handling or special procedures should be described. Include specific settings or other details needed for administration or deployment.
* If applicable, provide a description of the product usage for each participant and list equipment requirements for investigators. Include any participant preparation or anesthesia requirements.
* Provide a description of any specific medical or surgical procedures involved in the use of the investigational device with reference to the IDFU for device protocols for more detailed instructions.

<Start of common text>

1. The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants [randomized/assigned] to study intervention may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, [institution, the head of the medical institution (where applicable), or authorized site staff] is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the [study reference manual or other specified location].

<End of common text>

## Assignment to Study Intervention

* Describe method of assigning participants to study intervention. If participants will be assigned to intervention sequences as in a cross-over study, then describe these sequences. For complex designs, use of a table is recommended.
* Briefly describe the randomization procedures (eg, central randomization procedures), the method used to generate the randomization schedule (eg, computer generated), the source of the randomization schedule (eg, sponsor, investigator, or other), and whether or not an Interactive Voice/Web Response System (IVRS/IWRS) will be used. To maintain the integrity of the blind, do NOT include the block size.
* If adaptive randomization to intervention is to be used or if other methods of covariate balancing/minimization are employed, provide a cross link to the methods of analysis in Section 9 Statistical Considerations.
* State any other study-specific rules (eg, once a randomization number has been assigned, it must not be re-assigned).
* Include details of how and when a participant is allocated a participant number and the participant numbering convention, if relevant, in the Study Reference Manual.
  + Discuss any bias-reducing procedures if randomization is not used.
  + Include the stratification process and stratification variables, if applicable.

<Start of example text>

|  |  |
| --- | --- |
| **Type of Study** | Example text to use |
| **Study using IVRS/IWRS** | All participants will be centrally assigned to randomized study intervention using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.  Study intervention will be dispensed at the study visits as summarized in the SoA.  Returned study intervention should not be redispensed to the participants. |
| **Study using precoded randomization provided to site** | On Day [X], participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant’s assignment to one of the [X] arms of the study, according to the randomization schedule generated prior to the study by the statistics department at [sponsor/designee]. Each participant will be dispensed blinded study intervention, labeled with the participant’s unique randomization number, throughout the study. |

<End of example text>

## [Blinding, Masking]

* *Masking* or another appropriate synonym may be used in place of *blinding* if considered more appropriate in the context of the study or study population (eg, studies involving visually impaired participants), but maintain consistent use within the protocol.
* If study includes blinding, ensure to include details to whom the intervention is blinded for: *Single-blind* refers to studies in which participants are blinded to study intervention but site personnel (eg, monitors and investigators) and sponsor personnel are not. *Double-blind* refers to studies in which both participants and site personnel are blinded to study intervention.
* If someone involved in conducting the study is not blinded (eg, the site pharmacist or the sponsor’s clinical trial material group), describe the methods used to preserve the blinding of the other personnel conducting the study.
* Provide a description of the specific blinding procedures, if any, to be used. If blinding will not be used, include a statement to that effect.
* Describe how any blinding will be achieved and any impact on bias/randomization.
* Include the circumstances in which the blind will be broken for an individual or for all participants (eg, for SAEs), the procedures to be implemented to do this, and a description of who has access to participant codes. If the study allows for some investigators to remain unblinded (eg, to allow them to adjust medication), the methods of shielding other investigators should be explained.

<Start of example text>

|  |  |
| --- | --- |
| **Type of Study** | Example text to use |
| **Open-label, no blinding at site level** | This is an open-label study; potential bias will be reduced by the following steps: [central randomization, adjudications]. |
| **Open-label using central randomization via IVRS/IWRS** | This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by the following steps: [central randomization, adjudications]. |
| **Blind break (IVRS/IWRS)** | This is a double-blind study in which [participants/care providers/investigators/outcomes assessors, etc] are blinded to study intervention. The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants’ intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator’s discretion, contact the sponsor to discuss the situation prior to unblinding a participant’s intervention assignment unless this could delay emergency treatment for the participant. If a participant’s intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded. |
| **Open-label using blinded randomization** | This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using randomization envelopes. The site will receive blinded randomization envelopes that will be opened in ascending numerical order immediately prior to the start of study intervention administration for each participant. The site will record the date and time the envelope was opened.  **Note for open label**: This is not an approach to be supported from a statistical perspective. Open-label randomized studies need to use central randomization. If envelopes are preassigned to the site, the randomization must be blocked at the site level, which introduces selection bias risk whether or not the randomization codes are blinded in envelopes. |
| **Blind break (envelopes)** | This is a double-blind study in which [participants/care providers/investigators/outcomes assessors, etc] are blinded to study intervention. A sealed envelope that contains the study intervention assignment for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant’s intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator’s discretion, contact the sponsor to discuss the situation prior to unblinding a participant’s intervention assignment unless this could delay emergency treatment for the participant. If a participant’s intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the sponsor. |
| **Blinded study with unblinded third party who is dispensing intervention** | Participants will be randomly assigned in a [1:1] ratio to receive study intervention. Investigators will remain blinded to each participant’s assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.  This third party will instruct the [participant/participant’s parent(s) or legally authorized representative] to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.  In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately. |

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant’s intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

<End of example text>

## Study Intervention Compliance

* The measures that will be taken to ensure and document intervention compliance should be described (eg, intervention accountability records, diary cards, intervention concentration measurements, or medication event monitoring). May include the use of electronic data capture.
* Consider any implications of under/overdosing and crossreference Section 8.5 Pharmacokinetics if required.
* Teams should choose the appropriate wording from the options provided and delete the wording not used. For devices, participant compliance will depend on the device. Therefore, it should be described accordingly.

<Start of example text for studies using bulk supplies>

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

<End of example text for studies using bulk supplies>

<Start of example text when participants are dosed at the site>

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. [Study site staff will examine each participant’s mouth to ensure that the study intervention was ingested.]

<End of example text when participants are dosed at the site>

<Start of example text for study intervention(s) administered at home>

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by [direct questioning, counting returned tablets/capsules, etc] during the study visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of [insert study intervention(s)] dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

<End of example text for study intervention(s) administered at home>

## Dose Modification

* Procedures to be used for selecting/modifying an individual participant’s dose of study intervention should be described. Cross-reference Section 4.3 Justification for Dose as needed and do not repeat information already provided in that section. These procedures can vary from simple random assignment to a selected fixed intervention/dosage regimen to the use of a specified titration procedure or more elaborate response/toxicity-determined dose modification procedure (eg, dose is titrated upward at intervals until intolerance or some specified endpoint is achieved).
* Do not include information on stopping study intervention for individual participants due to safety/other reasons as this is detailed in Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal.
* If dose selection/modification decisions for individual participants are dependent upon review by a committee, include details in Appendix 10.1.6 Committees Structure and make a cross-reference here.
* Consider providing information in tabular format for simplicity.

If applicable, procedures for back-titration or dose reductions for toxicity should be described.

<Start of example text>

If a dose reduction is necessary, the study intervention will be administered as follows: [insert text or a table describing changes].

<End of example text>

### Retreatment Criteria

This section may be required in certain types of studies, eg, medical aesthetics. Any retreatment criteria needed after temporary discontinuation should be addressed in Section 7.1.4 Rechallenge.

<Start of example text>

All participants entered into the study will be treated at [Day X]. A participant may receive additional study interventions if the participant meets retreatment criteria as determined by the investigator and agrees to be retreated. Throughout the study, study intervention will be [blinded/unblinded].

After [Day X], the participant must meet all of the following criteria to be eligible for retreatment:

* [Criterion 1]
* [Criterion 2]

<End of example text>

## Continued Access to Study Intervention after the End of the Study

Include planned extension studies or possibilities for continued access to study intervention, if any, beyond completion of the study. Continued access should be clearly defined – differentiate between study-level and participant-level access.

If there is no intervention following the end of the study, then text should be included to state that this is the case. Describe any additional care that will be provided to participants after they complete or discontinue the study if this differs from what is normally expected for their condition.

## Treatment of Overdose

* Specify what is meant by study intervention overdose and any known antidote or nondrug therapies (see suggested text).
* Although clinical experience with overdose is often limited in early phases of development, provide any available project-specific guidance and information; however, ensure consistency with and avoid unnecessary duplication with any overdose information in the IB/IDFU/package insert. Cross-reference these documents if appropriate.
* Refer the investigator to the approved product label of the comparator (as applicable) for advice on overdose.

<Start of example text>

For this study, any dose of [study intervention] greater than [insert daily dose of study intervention] within a [24-hour] time period [± X hours] will be considered an overdose.

[Sponsor does not recommend specific treatment for an overdose.] OR [The antidote to study intervention is [X] and may be used in case of an overdose].

<End of example text>

<Start of common text>

In the event of an overdose, the [investigator/treating physician] should:

* Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
* Closely monitor the participant for any AE/SAE and laboratory abnormalities [as medically appropriate and at least until the next scheduled follow-up].
* [Obtain a plasma sample for PK analysis within [X] days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis)].
* [Document the quantity of the excess dose as well as the duration of the overdose.]

<End of common text>

## Prior and Concomitant Therapy

* Describe which interventions or procedures will be allowed before and during the study and any other specific rules and procedures related to permitted or prohibited concomitant therapy. If this list is lengthy consider including details in an appendix and cross-referencing here. Note that this section also includes surgical procedures for device protocols (cross-reference the device manual if included as an appendix).
* Minimize use of concomitant therapies or other co-interventions that can affect critical outcome measures to reduce potential imbalances in such co-interventions across study arms.
* Outline expectations for recording the use of concomitant therapies.
* Mention any non-investigational study interventions, such as background therapy or rescue medication, as applicable and provide details if appropriate.
* Include sponsor guidance, if any, on the management of study-specific conditions (eg, hyperkalemia, blood pressure control, edema, glucose control) that may need to be treated during the study.
* Review therapeutic area libraries for additional guidance.

<Start of example text>

Any [medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest] that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

* [Reason for use
* Dates of administration including start and end dates
* Dosage information including dose and frequency]

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

For healthy participant studies, consider using the suggested text beginning “Participants must abstain from taking prescription...”

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

[Paracetamol/Acetaminophen], at doses of [ 2 grams/day], is permitted for use [any time during the study, only during the screening period, etc]. Other concomitant medications may be considered on a case-by-case basis by the [investigator in consultation with the] medical monitor [if required].

<End of example text>

# Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Details should be kept at a minimum here. Include any actions to be taken if certain events are observed in an appendix and cross-reference that appendix as needed. Use schematics/algorithms if possible.

Details on replacement of dropouts should be described. If no replacement is planned, this should be stated.

<Start of common text>

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

<End of common text>

## Discontinuation of Study Intervention

For single-dose studies and some device studies, this section is not relevant. In such cases, state not *applicable* under Section 7.1.

Describe the criteria for discontinuation of the participant from study intervention. See the SoA for data to be collected at the time of discontinuation of study intervention. Make sure to collect (detailed) reasons for all discontinuations of investigational intervention in alignment with the estimands and /or plans to handle missing data.

As appropriate, consider using subheadings.

The following criteria should be considered for inclusion in each of the subsections:

* Liver chemistry – see Section 7.1.1 Liver Chemistry Stopping Criteria
* Cardiac changes (eg, QTc) – see Section 7.1.2 QTc Stopping Criteria
* Pregnancy: cross-reference Section 8.4.5. Pregnancy
* Other safety criteria (eg, AE, PK criteria) – cross-reference Section 6.5 Dose Modification if relevant and do not replicate information provided there
* Disease-state criteria (eg, progressive disease)

<Start of example text>

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for [X]. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

<End of example text>

### Liver Event Stopping Criteria

Liver injury – see participant libraries for proposed algorithm and text. Guidelines in the libraries are general and may be applicable to most clinical studies. Protocol authors should carefully evaluate if the liver-related stopping criteria are appropriate for the participant population and class of therapy evaluated in the clinical study and modify them, if needed.

<Start of common text for liver injury>

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined [in the algorithm] or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Insert appropriate algorithm from relevant library.

<End of common text for liver injury>

### QTc Stopping Criteria

Insert appropriate text from relevant library.

<Start of common text for cardiac changes>

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using [Bazett’s formula [QTcB] or Fridericia’s formula [QTcF]]) after enrollment, the investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

<End of common text for cardiac changes>

### Temporary Discontinuation

Include specifics around criteria for interrupting study intervention, what to do if the participant needs to stop study intervention, whether they will continue in the study, and whether all or specify which evaluations will be performed for the stated duration of the study. Details of any rechallenge after a safety related event should be included in Section 7.1.4 Rechallenge.

### Rechallenge

Include specifics around rechallenge, criteria for restarting study intervention, what to do if the participant needs to stop study intervention, whether they will continue in the study, number of rechallenges allowed during the study, and whether all or specify which evaluations will be performed for the stated duration of the study. Example of language to use for rechallenge after a liver event are provided and should be used if required.

#### Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

This section does not apply to single-dose studies.

<Start of common text if restart/rechallenge is NOT allowed>

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are not allowed.

<End of common text if restart/rechallenge is NOT allowed>

<Start of common text if restart/rechallenge IS allowed>

Study intervention [restart/rechallenge] after liver chemistry stopping criteria are met is allowed in this study. If the participant meets liver chemistry stopping criteria, do not [restart/rechallenge] the participant with study intervention unless:

* [Sponsor board] approval **is granted**
* Ethics and/or IRB approval is obtained, if required, and
* Separate consent for intervention [restart/rechallenge] is signed by the participant

NOTE: If study intervention was interrupted for suspected intervention-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and reconsented before resumption of dosing.

Refer to Appendix 6 Liver Safety: Suggestions and Guidelines for Liver Events for details on the [restart/rechallenge] process.

If [sponsor board] approval to restart/rechallenge the participant with study intervention is **not granted**, then the participant must permanently discontinue study intervention and may continue in the study for protocol-specified follow-up assessments.

<End of common text if restart/rechallenge IS allowed>

## Participant Discontinuation/Withdrawal from the Study

Describe the criteria for withdrawal of participants from the study. Make sure to collect (detailed) reasons for all discontinuations of investigational intervention in alignment with the estimands and /or plans to handle missing data.

<Start of common text>

* A participant may withdraw from the study at any time at the participant’s own request for any reason (or without providing any reason) without any negative consequences.
* A participant may be withdrawn at any time at the discretion of the investigator for safety, [behavioral, or compliance] reasons.
* At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
* The participant will be permanently discontinued from the study intervention and the study at that time.
* If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
* If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

<End of common text>

## Lost to Follow up

Include a brief section on how the study will define and address participants who were lost to follow-up to help limit the amount and impact of missing data. Describe the nature and duration of follow-up, including follow‑up after discontinuation of intervention, as appropriate.

Include the final bullet of common text when follow-up status of a participant is critical to study outcomes

<Start of common text>

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

* The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
* Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls, and if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record.
* Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
* [Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.]

<End of common text>

# Study Assessments and Procedures

* Describe the assessments and procedures required during each period of the study (eg, screening, Week 1).
* Give all details that are not obvious from the SoA (eg, time of admission to the study site).
* Specify how unscheduled visit(s) will be handled and documented if not noted in the SoA.
* If the study includes qualitative interviews (or exit interviews), describe these evaluations.
* Describe methods/training to ensure consistency across centers, use of participant diaries, instructions on timing/conditions of assessments, and if a specifically qualified person (eg, physician, psychologist) should be performing these assessments. Specify that the same person should perform each assessment whenever possible. The procedures used, including means of maintaining the blind and centralized readings and measurements, should be described fully.
* Specify if the study allows for standard-of-care procedures as baseline assessments.
* For medical devices, provide a summary of the necessary training and experience needed to use the device.
* All COA parameters should be fully integrated into the appropriate sections of the protocol.
* COA is an umbrella term encompassing different types of outcomes:
  + Patient-reported outcome (PRO) measures – reported directly from the participant without interpretation by a clinician or anybody else
  + Clinician-reported outcome (ClinRO) measures
  + Observer-reported outcome (ObsRO) measures
  + Performance outcome (PerfO) measures
* If COA measures are used, include instructions for the investigators regarding the following:
  + Training and instructions provided to participants related to completing the questionnaires
  + Participant supervision during COA administration
  + Processes and rules for questionnaire review for completeness
  + Documentation of how and when data are filed, stored, and transmitted to or from the study site should be noted in the protocol or provided in a separate document.
* If PRO measures are used, include the following information:
  + Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal timepoint or period of interest.
  + Describe the instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.
  + Indicate permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other).
  + When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available.
  + Provide a rationale for the PRO assessment time points, and justify if the initial assessment is not pre-randomization.
* Details for maximum volume for blood draw, individual blood draws, and volumes required should be included if appropriate to the study.
* Describe minimum requirements for equipment used for assessing primary endpoint, including calibration and frequency of calibration, eg, equipment should be calibrated according to manufacturer’s specifications or annually if no specifications exist.
* If a participant diary (paper or an electronic device) will be used to capture participant- or investigator-reported data, describe the steps to be taken to ensure that participants and/or investigators make entries according to the study design and not, for example, just before a study‑site visit when their reports will be collected.

<Start of common text>

* Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
* Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
* All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
* Procedures conducted as part of the participant’s routine clinical management [(eg, blood count)] and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
* In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
* [Safety/laboratory/analyte results] that could unblind the study will not be reported to investigative sites or other blinded personnel [until the study has been unblinded].
* Planned timepoints for all assessments are provided in the SoA.

<End of common text>

Include the maximum amount of blood collected from each participant over the duration of the study and if any repeat or unscheduled samples may be taken, as appropriate.

<Start of example text>

[The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed [X] mL.]

[Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.]

<End of example text>

## Administrative [and General/Baseline] Procedures

* List and describe administrative and general/baseline procedures outlined in the SoA that are not described in the subsequent sections (eg, medical history).

## [Efficacy and/or Immunogenicity] Assessments

* Clearly list and define the specific measurements and assessments (including tools, equipment, instruments/questionnaires, laboratory tests, etc, with calibration methods if appropriate) that will be used for assessing and recording the efficacy data.
* The results of each primary and secondary outcome measure are required to be reported in the CT Registry; therefore, each measure and associated visits at which it will be evaluated should be clearly identified (visits should be captured in the SoA). For each measure, give the reference (where possible) and describe how scoring will be accomplished.
* Instructions or protocols for specialized tests may be presented in an appendix; however, do not use copies of case report forms (CRFs), published questionnaires, or rating scales as an appendix, as these will need to be redacted before disclosure. Any of these documents used in the study should be included in the CRF or annotated CRF with those not owned by the sponsor in a separate section for ease of redaction.
  + If any scale/questions are to be included in an appendix, it should be representative of what will be used in the CRF as it may change prior to study initiation or throughout the study. Consider including the following language in this section to address this circumstance, “Appendix [X] provides a representative example of the [scale] [questions] [specify other] that will be used in this study”.
* Any definitions used to characterize outcomes (eg, criteria for determining occurrence of acute myocardial infarction, designation of the location of the infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between transient ischemic attack and stroke, assignment of cause of death) should be explained in full.
* If categorical responses (global scales, severity scores, responses of a certain size) will be used in analyzing responses, they should be clearly defined.

## Safety Assessments

For each safety assessment:

* Specify how to perform, collect, and record each assessment (including tools, equipment, instruments/questionnaires, laboratory tests, etc, with calibration methods if appropriate); any limitations on personnel performing the assessment (eg, qualifications and training needed to conduct/interpret assessments, if an attempt should be made for the same individual to conduct that assessment throughout the study); and any definitions used to characterize outcomes.
* Specify methods used to standardize and/or interpret the assessment (eg, use of central laboratory, Holter monitoring, central ECG reader). Details can be provided in a separate document if they do not impact participant safety.
* Identify any noninvestigator party responsible for evaluation of laboratory or other safety assessments (eg, sponsor or external independent data monitoring committee) and describe any procedures used, including centralized reading/measurement.
* Include any questionnaires and rating scales used to classify laboratory or other safety assessments. Cross-reference Section 7 if linked with stopping criteria. Use validated scales. Reference the publication of the validation of the scale.
* Instructions or protocols for specialized tests may be presented in an appendix; however, do not use copies of CRFs, published questionnaires, or rating scales as an appendix, as these will need to be redacted before disclosure. Any of these documents used in the study should be included in the CRF or annotated CRF with those not owned by the sponsor in a separate section for ease of redaction.
  + If any scale/questions are to be included in an appendix, it should be representative of what will be used in the CRF as it may change prior to study initiation or throughout the study. Consider including the following language in this section to address this circumstance, “Appendix [X] provides a representative example of the [scale] [questions] [specify other] that will be used in this study”.
* Include guidelines for the management of relevant laboratory or other safety assessment abnormalities.
* Carefully evaluate inclusion/exclusion and withdrawal criteria to ensure any assessments required are included in the list of required tests. For example, Child-Pugh assessment requires measurement of albumin for calculation; thus, albumin needs to be included in the clinical chemistry parameters.
* Pregnancy testing and ECG monitoring should be included in safety evaluations regardless of whether they are collected only at baseline to determine eligibility or if they are repeated throughout the study.

### Physical Examinations

* Consider further specifications (eg, for height and weight measurements, the participant is allowed to wear indoor, daytime clothing with no shoes) if appropriate for the study.
* Include special instructions for assessing weight changes that may require dose adjustments. If the dose will be adjusted based on weight, provide details in Section 6 Study Intervention(s) and Concomitant Therapy.

<Start of example text>

* A complete physical examination will include, at a minimum, assessments of the [cardiovascular, respiratory, gastrointestinal, and neurological] systems. Height and weight will also be measured and recorded.
* A brief physical examination will include, at a minimum, assessments of the [skin, lungs, cardiovascular system, and abdomen (liver and spleen)].
* Investigators should pay special attention to clinical signs related to previous serious illnesses.

<End of example text>

### Vital Signs

* Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected.
* Include any specific instructions with respect to the collection and interpretation of vital signs. If orthostatic vital signs will be assessed, include instructions for supine and standing blood pressure and pulse measurements.
* Select the standard methods of vital sign collection as appropriate for the countries in which the study will be conducted.
* For studies requiring sensitive blood pressure monitoring (eg, if blood pressure decrease or increase is an anticipated effect), include details on device calibration requirements or frequency of measuring.

<Start of example text>

* [Oral] [Tympanic] [Rectal] [Axillary] [Skin] [Temporal artery] temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).
* Blood pressure and pulse measurements will be assessed [specify participant’s position, if applicable] with a completely automated device. Manual techniques will be used only if an automated device is not available.
* Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
* For blood pressure measurements, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure readings will be recorded.

OR

* Vital signs will be measured in a [specify participant’s position, if applicable] position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse [and respiratory rate]. [Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.]

<End of example text>

### Electrocardiograms

* Specify if the ECG is for screening purposes only.
* Include any specific instructions for the collection and interpretation of ECGs (eg, time points relative to dosing with study intervention or other evaluations).
* Indicate whether single or triplicate ECGs will be collected at each time point. If triplicate ECGs will be collected, provide necessary details.
* If ECGs will be analyzed at a central laboratory, instructions for the collection (eg, equipment), transmission, and archiving of ECG data should be agreed upon with the central laboratory and summarized. The turnaround time for safety alerts from the central laboratory to the study site should be specified.
* If ECGs will be read locally, indicate if digital ECG waveforms will be centrally archived and in what format. If the digital waveforms will be archived, there is no need to retrieve paper ECGs from the study sites.
* Include instructions with respect to local review of ECG tracings for safety findings, even if ECGs will be analyzed at a central laboratory, and any actions to be taken in response to ECG findings.
* Consider consultation with the relevant sponsor cardiovascular safety committee.
* High-quality ECG data should be collected if the goal is to assess the effects of study intervention on ECG intervals such as the QT interval. Such ECG data may be required to meet regulatory authority expectations for a thorough ECG assessment (eg, as outlined in ICH E14) or to better assess a cardiac conduction signal from previous nonclinical or clinical studies. High‑quality ECGs are typically performed more frequently and in a more rigorous and more standardized fashion than routine ECGs. High-quality ECGs are typically recorded and archived in digital format using a central ECG vendor and analyzed by a specialized central laboratory.
* The frequency and timing of high-quality ECGs should reflect the PK of the study intervention and any metabolites. In general, ECGs should be conducted around key PK timepoints including the following: predose, maximum observed concentration (Cmax) after the first dose, and steady‑state Cmax. Additional measurements should be performed to account for potential PK differences between participants, unanticipated drug metabolites, delays between peak plasma/serum and tissue concentrations, and a PK lag effect. When possible, time-matched measurements should be considered (eg, collection of predose and postdose ECGs at a similar time of day) to minimize the effects of diurnal variation in ECG intervals.
* If high-quality ECG data are not collected in the study, ECG data must still be collected for routine safety monitoring of participants, at least until important study intervention effects on cardiac conduction or cardiac function have been sufficiently excluded in clinical studies. For studies investigating long-term dosing, ECGs should be obtained throughout the course of the study (eg, after each cycle of study intervention or monthly) as well as at the completion of the study.
* Ensure the correction formula listed here is consistent with that listed in the QTc exclusion and withdrawal criteria.
* Include the second bullet of suggested text if triplicate ECGs are to be obtained.

<Start of example text>

* [Triplicate OR Single] 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals. Refer to Section 7.1.2 for [QTc] withdrawal criteria and any additional [QTc] readings that may be necessary.
* [At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.]

<End of example text>

### Clinical Safety Laboratory Tests

* For multicenter studies in participants who are patients, make every effort to ensure routine laboratory safety tests are performed by a central laboratory. If local laboratory tests are required, these must be stated clearly in the protocol. Provisions should be in place to allow for the acceptance of local laboratory data (even if a central laboratory is used). Sponsor databases should be set up appropriately for the reporting of data from both central and local laboratories. Consult with the data management representative for language to be included on how data should be reported to the sponsor if a local laboratory is used.
* Specify if the use of local laboratories is allowed in cases where initiation of study intervention or safety follow-up is time sensitive and the central laboratory results will not be available before the need to begin study intervention or other actions that need to be taken for safety reasons.
* Specify any special instructions for screening samples.
* Specify which laboratory parameters should be included in each panel (eg, for hematology, chemistry, urinalysis). List only those that will be analyzed for the study. Confirm lists and blood volumes before finalizing the protocol.
* See therapeutic area libraries for additional guidance.

<Start of common text>

* See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
* The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
* [Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant’s condition].
* All laboratory tests with values considered clinically significantly abnormal during participation in the study or within [insert timeframe] after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  + [If clinically significant/any] values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  + All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  + If laboratory values from non-protocol-specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded.

<End of common text>

### Pregnancy Testing

* Include the defined timepoints for pregnancy testing in CBP participants in the SoA. Timepoints should be based upon a risk assessment of the potential for genotoxicity and teratogenicity/fetotoxicity of the intervention(s) in the study. Risk should be determined for each intervention with input from the company’s nonclinical safety assessment group. Determination of risk for a marketed compound should also consider the risks outlined in the product label. Further guidance can be found in International Council for Harmonization [ICH] Guideline M3(R2) and Clinical Trial Facilitation Group (CTFG). At a minimum, a pregnancy test should be performed at screening and at the end of relevant systemic exposure to confirm pregnancy status. Additional testing may be required between the screening visit and the first dose of study intervention on Day 1. Consider additional pregnancy testing if the interval is:
  + ≤ 4 days, a repeat highly sensitive serum pregnancy test usually is not required
  + > 4 days, a repeat serum pregnancy test should be obtained
* For studies that have requirements for multiple pregnancy tests, add additional criteria as needed (eg, if there is a requirement for a test to be performed within a proximal timeframe prior to first dose, specify as inclusion criteria; if at a specified visit, or at the end of study intervention, note in the SoA and provide any necessary details here).
* A serum pregnancy test may diagnose pregnancy ~6 to 10 days after fertilization; a urine pregnancy test, because it is less sensitive, will diagnose pregnancy a few days after a serum pregnancy test. As serum pregnancy tests have a lower detection limit and will detect pregnancy closer to the date of conception, serum testing is the preferred test if there is a requirement to know pregnancy status within a few days of the first dose of study intervention.
* Decide if local or central testing will be standard for the protocol. Highly sensitive serum testing is mandatory if required by local regulations or the IRB/IEC, or to resolve an indeterminate test or confirm a positive urine test.
* Consider adding a generic sentence to the protocol that additional pregnancy tests will be conducted if required by local regulations.

Insert library content here.

### Suicidal Ideation and Behavior Risk Monitoring

Clinical studies meeting either of the following 2 criteria must include appropriate assessments (eg, Columbia-Suicide Severity Rating Scale [C-SSRS]) to enable the prospective monitoring of suicidal ideation and behavior (SIB) in individual participants:

1. Patient or healthy volunteer studies using compounds that:

* are known to be active in the human central nervous system (CNS), or
* are being studied for CNS activity, or
* are being developed for any psychiatric or neurologic indication, or
* may affect mood, cognition, or behavior via their effects on the CNS (directly or indirectly), or
* are pharmacologically similar to medicines that have had SIB reported in association with their use, which is considered to be at least possibly causally associated (eg, isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation medicines and medicines for weight loss).

2. Studies including any participant population with an elevated risk of SIB, which may manifest during the study, and for which monitoring of SIB is considered to be in the best interest of participant safety and/or science.

Notes:

* Determination and documentation is made at a program level on a company-specific basis according to their practices. Assessment of SIB is difficult in participants with cognitive impairment of a degree that interferes with understanding of the concept of suicide (eg, Alzheimer’s disease, other dementias, learning disability, autism), and in participants who are terminally/critically ill. It is therefore reasonable to omit in these circumstances. If omission of SIB assessment is being considered for studies in challenging populations that would otherwise meet the criteria for monitoring, regulatory authority approval should be sought prior to protocol approval.
* Young children may not have reached sufficient cognitive maturity to understand the concept of death. As there is also no validated instrument for the prospective monitoring of SIB in children less than 7 years of age, all proposed studies in children less than 7 years that meet the criteria for monitoring of SIB should therefore be referred for regulatory and company’s internal review/advisory board for approval prior to protocol approval.
* It should be recognized that in uncontrolled studies, scientific interpretation of the results of monitoring of SIB may be difficult or impossible. Even so, if monitoring is important for participant safety it may be included.

<Start of example text>

[STUDY INTERVENTION] is considered to be a CNS-active intervention.

AND/OR:

[STUDY INTERVENTION] is related to products with an increased risk of suicidal ideation or behavior.

AND/OR:

Patients with [CONDITION] may occasionally develop suicidal ideation or behavior.

<End of example text>

<Start of common text>

Participants being treated with [study intervention X] should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

<End of common text>

If study design calls for family and caregiver input, specify the need to communicate to these parties. For wording to be used in pediatric studies, see the pediatric participant library.

Specify how, if in the event of suicidal ideation or behavior, information will be shared with the legal guardian or others, including mental health professionals (local regulations should be followed). Address in the informed consent and assent forms as appropriate.

<Start of common text>

When informed consent or assent has been given, families and caregivers of participants being treated with [study intervention X] should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

[Baseline assessment of suicidal ideation and behavior/intervention-emergent suicidal ideation and behavior] will be monitored during [study identifier] using [name of scale].

<End of common text>

## Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

* The means of obtaining AE data should be described (volunteered, checklist, or questioning) as should any specific rating scales used and any specifically planned follow-up procedures for specific AEs or any planned rechallenge procedures in case study intervention is discontinued because of an AE.
* If the study requires solicited and unsolicited adverse events to be collected then include the optional text in Section 8.4.1 and the optional table of definitions in Appendix 3.
* Consider whether there are any protocol-specific events that may need expedited reporting, or alternatively, are not required to be reported. Provide guidance for investigators. If there is a specific AE that will be of special interest it should be described in Section 8.4.8.

**NOTE: Level 3 headings** **in this section from 8.4.1 to 8.4.5 are common text and must be maintained to ensure the elements required by ICH and regulators are included in the protocol.**

<Start of common text>

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix [3/7].

[The definitions of unsolicited and solicited adverse events can be found in Appendix 3].

[The definitions of device-related safety events, adverse device effects (ADEs), and serious adverse device effects (SADEs) can be found in Appendix 7. Device deficiencies are covered in Section 8.4.9.]

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up [all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the [study intervention] [study]] (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix [3/7].

### Time Period and Frequency for Collecting AE and SAE Information

The first 2 paragraphs may be combined if the collection interval is the same for AEs and SAEs.

All SAEs will be collected from the [signing of the informed consent form (ICF) OR start of study intervention] until [the follow-up visit] at the timepoints specified in the SoA (Section 1.3).

All AEs will be collected from the [signing of the ICF OR start of study intervention] until [the follow‑up visit] at the timepoints specified in the SoA (Section 1.3).

[Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs].

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix [3/7]. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

See Section 8.4.5 for the time period for collecting pregnancy information and duration of follow-up of the pregnancy, if required.

### Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

For some studies, participants are not always able to provide valid verbal responses to open-ended questions. In these circumstances, another method of detecting AEs and SAEs must be specified.

### Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs [and AEs of special interest (as defined in Section 8.4.8)] will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix [3/7].

### Regulatory Reporting Requirements for SAEs

For all studies except those using medical devices also include the last bullet.

* Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
* The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
* An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [IB/IDFU/package insert or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.
* [Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators within 15 days.]

NOTE: There may be incidences where events are potential efficacy endpoints, eg, in MACE studies. It is standard practice to exclude them from SAE reporting unless deemed possibly related to study intervention as long as this has been agreed up front with all of the relevant regulatory agencies. These events should be detailed in Section 8.4.7.

<End of common text>

### Pregnancy

* Define the time period for collecting pregnancy information for female participants or female partners of male participants as appropriate (eg, class effects, evidence from animal reproduction). This should align with the time period for postintervention contraception as described in Section 5.1.
* Do not collect pregnancy information for participants known to be pregnant during the screening period or before exposure to study intervention unless these participants enter the study, in which case consider whether pregnancy history needs to be collected.
* Specify any additional actions required (discontinuation of study intervention, withdrawal from the study, unblinding), and any assessments that need to be performed. Align all discontinuation criteria included here with Section 7.1.
* For certain types of study intervention (eg, gene therapy), prolonged follow up of the newborn (the terms newborn and neonate are used interchangeably per the ICH definition) may be required. The protocol should specify all relevant details for this follow up including the duration of that observation period. The ICF needs to cover all applicable aspects for this follow up.

<Start of common text>

* Details of all pregnancies in [participants able to give birth and, if indicated, participants’ partners able to give birth] will be collected after the start of study intervention and until [time period for reporting pregnancies should align with the time period for postintervention contraception determined in Section 5.1].
* If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor [within 24 hours] of learning of the [participant or participant’s partner (after obtaining the necessary signed informed consent from the participant’s partner)] pregnancy.
* While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
* Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
* The investigator will collect follow-up information on the [participant/pregnant partner], the pregnancy outcome, and the neonate. The information will be forwarded to the sponsor.
* Any poststudy pregnancy-related SAE in the mother or SAE in the newborn, if considered reasonably related to the study intervention by the investigator, will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former [study participants/pregnant partner], they may learn of an SAE through spontaneous reporting.
* Any participant who becomes pregnant while participating in the study [will discontinue study intervention or be withdrawn from the study] OR [may continue study intervention at the discretion of the investigator.]

<End of common text>

Should a participant become pregnant during the course of a study, under certain circumstances the study design may allow for the continuation of study intervention. The protocol should include details regarding what must occur prior to allowing continuation for that participant. In these instances, ICH guidelines and local regulations must be observed, and appropriate justification is needed. In the absence of such justification participants who become pregnant must be discontinued from study intervention.

Justification for continuation of study intervention may include the following circumstances:

1. The study intervention has an approved label that indicates it can be used safely in pregnant individuals.
2. The participant has a high-mortality disease and the investigator determines the participant is benefiting from study participation and there is no other alternative treatment for the participant.
3. The investigator, after careful individual assessment, confirms a positive benefit-risk ratio.

Depending on local regulations further follow up of the newborn after delivery for potential effects of the study intervention may be required, see the Initiatives & Regulatory Landscape Assessment Output.

<Start of example text>

Prior to continuation of study intervention during the pregnancy, the following must occur:

* The sponsor and the relevant IRB/IEC give written approval.
* The participant gives signed informed consent.
* The investigator agrees to monitor the outcome of the pregnancy, including the status of the participant and their offspring.
* The investigator agrees to monitor the development of the offspring as locally required.

<End of example text>

### Cardiovascular and Death Events

### Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Specify if applicable any disease-related events (DREs) and/or disease-related outcomes that do not need to be reported as AEs or SAEs.

<Start of example text>

The following disease-related events (DREs) are common in participants with [disease, condition under study] and can be serious/life threatening:

* [Event A
* Event B
* Event C
* Event D]

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded within [the appropriate timeframe]. [These DREs will be monitored by a/an [independent data monitoring committee, safety review committee, safety review team, other] on a routine basis. See Section 10.1.6]

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

The event is, in the investigator’s opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

<End of example text>

### Adverse Events of Special Interest

Consult the appropriate medically qualified team member if unsure if this section is applicable for a particular protocol.

The description should include the following:

* The definition of the event
* Is it a measurable quantity? If yes, how will the measurement be done?
* If it is a clinical event, how will it be confirmed?

### Medical Device Deficiencies

This section is required for a study in which a medical device is provided for use in the study (ie, there are medical devices listed in Section 6.1.1 that are manufactured by the sponsor or by a third party for the sponsor). If Section 6.1.1 only includes nonsponsor medical devices, then this section is not needed.

* Instructions for documenting medical device deficiencies are provided in Appendix 7.

<Start of common text>

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Appendix 7 of the protocol.

#### Time Period for Detecting Medical Device Deficiencies

* Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
* If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 7.

#### Follow-up of Medical Device Deficiencies

* Follow-up applies to all participants, including those who discontinue study intervention.
* The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
* New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

#### Prompt Reporting of Device Deficiencies to the Sponsor

* Device deficiencies will be reported to the sponsor within [24 hours] after the investigator determines that the event meets the protocol definition of a medical device deficiency.
* The medical device deficiency report form will be sent to the sponsor by [method]. If [method] is unavailable, then [alternative method] should be utilized.
* The sponsor will be the contact for the receipt of device deficiency reports.

#### Regulatory Reporting Requirements for Device Deficiencies

* The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
* The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

<End of common text>

## Pharmacokinetics

* Insert text as appropriate for this study. If population PK will be included, provide appropriate text. If PK will not be part of the study, include a statement to this effect.
* Describe any study intervention concentrations to be measured and the sample collection times relative to dosing. Samples of plasma, urine, or other fluids may be taken for the purpose of measuring compliance, adjusting dose, or determining if a therapeutic window exists. This section of the protocol will be written in collaboration with the appropriate PK representatives and will contain information about sampling times, sample volume, sample handling procedures, assay methods, etc. Specific sample collection and processing including retention time instructions can be described in an appendix and cross-referenced.
* Indicate definitions for the PK parameters (eg, area under the curve [AUC], maximum observed concentration [Cmax], time to Cmax [Tmax], half-life [T½], volume of distribution [Vd], clearance [CL]) of interest and how they will be calculated. Consult with the PK representative for this information.
* Describe sampling time relative to ingestion of food, posture, and possible effects of concomitant medications/alcohol/caffeine/nicotine.
* Describe the biological sample(s) collected (blood, urine, or other such as breath, saliva, biopsies, etc), the handling of samples, and the assay method including references to published and/or internal assay validation documentation.
* Specify other factors that are important in assessing the PK of the study intervention (eg, soluble circulating receptors, renal or hepatic function) and the plan for measuring these factors.
* Do not reiterate the details given in the SoA or other sections of the protocol. Use cross-references as needed.
* If samples remaining after the pharmacokinetic analysis may be used for future exploratory research, describe here or include a separate section for future research and cross-reference. Describe participant consent process for use of leftover samples, the potential objective of future research and handling of future analysis (eg, in a separate report and not the integrated CSR).

<Start of example text>

* [PK parameters are not evaluated in this study].

<End of example text>

OR

<Start of example text>

* [Plasma/serum/whole blood/urine] samples of approximately [X] mL will be collected for measurement of [plasma/serum/whole blood/urine] concentrations of [study intervention/other] as specified in the SoA (Section 1.3) [specify timepoints only if not obvious from the SoA].
* A maximum of [X] samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
* Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
* Samples will be used to evaluate the PK of [study intervention]. Each [plasma/serum/whole blood] sample will be divided into [X] aliquots (1 each for [PK, other analyses, and a backup]). Samples collected for analyses of [study intervention (plasma/serum/whole blood)] concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
* Genetic analyses will not be performed on these [plasma/serum/whole blood] samples [unless consent for this was included in the informed consent]. Participant confidentiality will be maintained. At visits during which [plasma/serum/whole blood/etc] samples for the determination of [multiple aspects] of [study intervention] will be taken, one sample of sufficient volume can be used.

If there are blinded study intervention concentration results, consider adding the relevant suggested text.

* Intervention concentration information that [may/would] unblind the study will not be reported to investigative sites or blinded personnel [until the study has been unblinded].

<End of example text>

## Pharmacodynamics

* Insert text as appropriate for this study. If pharmacodynamics will not be part of the study, include a statement to this effect.
* This section of the protocol will be written in collaboration with the appropriate functional area representatives and will contain information about sampling times, sample volume, sample handling procedures, assay methods, etc. Specific sample collection and processing including retention time instructions can be described in an appendix and cross-referenced.
* Describe sampling time relative to ingestion of food, posture, and possible effects of concomitant medications/alcohol/caffeine/nicotine.
* Describe the biological sample(s) collected (blood, urine, or other such as breath, saliva, biopsies, etc), the handling of samples, and the assay method including references to published and/or internal assay validation documentation.
* Do not reiterate the details given in the SoA or other sections of the protocol. Use cross-references as needed.

## Genetics

* If this will not be part of the study, include a statement to this effect.
* Contact the appropriate sponsor functional area representatives to ensure that appropriate genetic study design text is included throughout the protocol.
* See the appropriate guidelines/templates from the sponsor functional area representatives (eg, standard attachments for shipping and handling of laboratory samples). Dependent upon the volume of these attachments, they may be added to the protocol in an appendix or provided in supplementary documents that will accompany the protocol.

<Start of example text>

Genetics are not evaluated in this study.

<End of example text>

OR

<Start of example text>

A [X] mL [blood OR saliva] sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

[See Appendix [5 Genetics] for information regarding genetic research]. Details on processes for collection and shipment and destruction of these samples can be found in [specify location].

<End of example text>

## Biomarkers

If biomarkers will not be evaluated, include a statement to this effect. Do not delete the heading.

<Start of example text>

Biomarkers are not evaluated in this study.

<End of example text>

OR

If biomarkers will be evaluated:

* Indicate the biological samples that will be collected (eg, serum, plasma, etc).
* Indicate the types of biomarkers that will be studied. For primary/secondary endpoints, specify biomarkers to be assessed. For exploratory biomarkers, there does not need to be a complete list of every biomarker, but the nature of the markers that may be measured, eg, inflammatory biomarker, including but not limited to TNFa, IL-6 etc. NOTE: Each matrix/endpoint will require its own paragraph as shown in the suggested text.
* Specify the retention time for the samples (this must match the information in the ICF; typically 15 years although country-level legislation may limit this) and that samples may be used for further research if consent is provided.
* If RNA-sequencing (RNA-Seq) is planned, ensure that this is specified in the consent.
* If instructions for collection of samples are complex, then consider including them in an appendix or laboratory manual rather than the main text of the protocol.

<Start of example text>

* [Specify type of sample, eg, plasma] samples will be collected to [protocol-specific objective]. Biomarkers will include [biomarker names]. Samples will be collected according to the schedule described in the SoA and as detailed in [laboratory manual provided separately to sites].
* [Specify type of sample, eg, blood] samples will be collected to [protocol-specific objective]. Biomarkers will include [biomarker names]. Samples will be collected according to the schedule described in the SoA and as detailed in [laboratory manual provided separately to sites].
* [Sponsor] may store samples for up to [X] years after the end of the study to achieve study objectives. Additionally, with participants’ consent, samples may be used for further research by [sponsor] or others such as universities or other companies to contribute to the understanding of [specify disease targeted in protocol] or other diseases, the development of related or new treatments, or research methods.

<End of example text>

## Immunogenicity Assessments

If immunogenicity assessments are included as an efficacy or safety objective, then cross-reference Sections 8.2 or a subsection of Section 8.3 and mark this section as not applicable. For other assessments to be used for research purposes, use the suggested text.

<Start of example text>

Antibodies to [study intervention] will be evaluated in [plasma/serum] samples collected from all participants according to the SoA. Additionally, [plasma/serum] samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor’s designee.

[Plasma/Serum] samples will be screened for antibodies binding to [study intervention] and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to [study intervention] and/or further characterize the immunogenicity of [study intervention].

The detection and characterization of antibodies to [study intervention] will be performed using a validated assay method by or under the supervision of the sponsor. [All samples collected for detection of antibodies to study intervention] will also be evaluated for [study intervention] serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of [X] years (or according to local regulations) following the last participant’s last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to [study intervention].

<End of example text>

## [Health Economics OR Medical Resource Utilization and Health Economics]

If this section is not applicable, include a statement to this effect.

* This section does not apply to COAs (for COAs cross reference the instructions in the efficacy and safety sections).
* Include this section only for any value evidence and outcomes assessment not included in either the efficacy or safety sections.
* Briefly describe the health outcome measures, collection method (eg, diary, physician interview), and participant burden.

<Start of example text>

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

<End of example text>

OR

<Start of example text>

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will

* Include the reasons and duration of hospitalizations and emergency room visits and
* Exclude procedures, tests, and encounters mandated by the protocol.

The sponsor may use the collected data to conduct economic analyses.

<End of example text>

# Statistical Considerations

Provide a statement on when the main analysis and reporting will be made.

<Start of example text>

The analysis and reporting will be done on all data from all participants at the time the study ends.

<End of example text>

<Start of example text>

The statistical analysis plan will be finalized prior to [unblinding/unmasking/first participant first visit/database lock] and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important [endpoints/estimands] including primary and key secondary [endpoints/estimands].

<End of example text>

## General Considerations

This section should describe general methods and definitions that do not need to be repeated in the subsequent sections. For example, a general statement that all investigational intervention/treatment condition comparisons for all categorical analyses will be tested using Fisher’s exact test does not need to be repeated for each categorical analysis described in later subsections. The same would be true for analysis of variance information and the model used. If different definitions are required for specific analyses, these should be stated in the relevant section. Suggested topics to be included in this section, if appropriate for the study, are provided. Subsections can be used, if applicable. Below example headings are given, but sections can be deleted, added, or modified as needed. If subsections are used, this section can have the section heading only, with no text required.

* Common definitions of baseline
* For randomized studies, describe stratification factors if applicable, and if not specified in Section 4.1
* General methods, such as handling of wrong stratification, wrong investigational intervention assignment, handling of values below lower limit of quantification, continuous variables will be summarized with min, max, mean, median, standard deviation, quantiles, etc
* General choice of analysis sets for analyses.
* Pooling strategies for countries/regions, sites, etc
* Strategy for grouping study arms, eg, combining all active dose arms versus control.
* Definition of study periods if needed.
* Definition of which contrasts between investigational interventions/treatment conditions will be provided.
* For studies conducted under a master protocol, include details regarding whether analyses will be conducted by combining sub-studies or within a sub-study.

### [Decision Criteria/Statistical Hypotheses]

* Decision criteria, such as nominal significance levels, 1- or 2-sided tests, and confidence interval probabilities
* Clearly articulate the statistical hypotheses (null and alternative hypotheses), that will be the subject of statistical testing related to each key/confirmatory estimand, when applicable. It is recommended to state both the formal statistical null and alternative hypotheses and a textual non-technical description. In case no hypotheses are planned to be tested, state this in this section.
* If Bayesian or estimation approaches (no formal hypothesis) are used, describe the decision rule or estimation method.
* For non-inferiority tests, the non-inferiority margin should be justified.

<Start of example text>

Example 1:

The primary objective is to demonstrate that [test intervention] is superior to [control] in achieving [outcome] at [timepoint]. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows:

* Null hypothesis: [test intervention] is not different from [control] with respect to the achievement of [outcome] at [timepoint].

vs.

* Alternative hypothesis: [test intervention] is different from [control] with respect to the achievement of [outcome] at [timepoint].

The null and alternative hypotheses corresponding to the secondary estimands are as follows:

Secondary objective [1]:

* Null hypothesis: [test intervention] is not different from [control] with respect to the achievement of [outcome/endpoint] at [timepoint].
* Alternative hypothesis: [test intervention] is different from [control] with respect to the achievement of [outcome] at [timepoint].

Secondary objective [2]:

* Null hypothesis: [test intervention] is not different from [control] with respect to change from baseline to [timepoint] in [health measurement/outcome].
* Alternative hypothesis: [test intervention] is different from [control] with respect to change from baseline to [timepoint] in [health measurement/outcome].

Example 2:

For the primary estimand with primary endpoint, change from baseline to [timepoint] in [health measurement or observation], the following 2 (confirmatory) 1-sided hypotheses are planned to be tested for [test intervention] versus [control]. Let the mean treatment difference be defined as μ = ([test intervention] minus [control]). Note that smaller values for [endpoint] are better.

The primary aim is to show that the [test intervention] is not unacceptably worse than the existing [control], using a non-inferiority margin of [non-inferiority margin] [unit] for the difference of the means. If this is confirmed, a test for superiority will subsequently be made.

Noninferiority (noninferiority margin is [noninferiority margin])

H0: μ ≥ [noninferiority margin] against Ha: μ < [noninferiority margin]

The rationale for the non-inferiority margin is…

Superiority

H0: μ ≥ 0.0 [unit] against Ha: μ < 0.0 [unit]

Operationally the hypotheses will be evaluated by 2-sided tests.

<End of example text>

### Multiplicity Adjustment

* Clearly state the (local and/or global) significance level, the family-wise error-rate and the method for controlling overall type I error.

<Start of example text>

Example 1 (linked to example 1 in the statistical hypotheses):

A closed testing procedure that controls the family wise error rate in the strong sense at the overall [5]% level will be applied. The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be carried out in the hierarchical order as indicated in Section 9.1. This means that the statistical hypotheses are tested in the prespecified order at the same significance level of α = [0.05] as long as all preceding hypotheses are rejected. Once a hypothesis is not rejected, subsequent hypotheses cannot be formally tested and therefore cannot be rejected.

Example 2 (linked to example 2 in the statistical hypotheses):

The type I error of α= [5]% will be controlled in the strong sense using a hierarchical (fixed sequence) testing procedure. This is based on priority ordering of the null hypotheses and testing them in this order using the [2]-sided [95]% confidence interval approach until an insignificant result appears. Consequently, the second null hypothesis will only be tested if the first null hypothesis has been rejected in favor of [test intervention]. Operationally the hypotheses will be evaluated by 2-sided tests.

The steps in the hierarchical testing procedure are as follows:

Step 1: [health measurement or observation] noninferiority of [test intervention] versus [control]

Step 2: [health measurement or observation] superiority of [test intervention] versus [control]

<End of example text>

### Impact of Intercurrent Events Strategies

* For studies with estimands,
  + Consider adding a subsection to describe the intercurrent events, their strategies, and any technical statistical implication. Alternatively, this can be described in the relevant analysis sections.
  + Describe how intercurrent events will be summarized (number by treatment condition and timing).

### Handling of Missing Data

Consider adding a subsection on handling of missing data including missing baseline values if this is planned to be handled in the same way across analyses. Alternatively, this can be described in the relevant analysis sections.

## Analysis Sets

* This CPT uses the following terminology:
  + ‘Participant Analysis Set’ = set of study participants. Examples: all randomized study participants, full analysis set, safety analysis set.
  + ‘Data Points Set’ = the set of data points from each participant to be included in the analysis considering their (relative) timing as well as the occurrence of intercurrent events. Example: data points obtained while the participant was exposed to investigational intervention, i.e, data points collected at or after the start and up to the stop date of investigational intervention + 2 calendar days.
  + ‘Analysis Data Sets’ = the set of data points to be included in the analysis in a set of study participants, ie, combination of ‘Data Points Set’ and ‘Participant Analysis Set’.
* Regardless of whether estimands are explicitly defined in Section 3 of the study protocol, the sets of participants included in statistical analyses, ie, ‘Participant Analysis Sets’, should be defined. The number of participant analysis sets should be minimized.
* In addition, it will often be helpful to define which measurements on a selected set of participants are to be in- or excluded in a specific analysis. In studies describing estimands, the treatment effect of interest is defined in a way that guides both the set of participants and the relevant observations from each participant to be included in the estimation in relation to the occurrence of intercurrent events.
* The selection and identification of the “to-be-analyzed data points” for a set of participants can be achieved by defining ‘Data Points Sets’ as required for the analyses.
* The description of the assignment of participants to intervention in the analysis (“as randomized” or “as actually received”) can be described in this section or in Section 9.3.
* Note, naming of the Participant Analysis Set and not only the full data set (participants and data points) is recommended for ease of programming.
* Three examples are provided for illustrative purposes only. Other formats, other definitions, and different naming conventions can be used.

<Start of example text>

Example 1:

For the purposes of analysis, the following analysis sets are defined:

| **Participant Analysis Set** | **Description** |
| --- | --- |
| Full analysis set (FAS) | * All randomized participants. |
| Safety analysis set (SAS) | * All participants who are exposed to investigational intervention. |

The full analysis set will be used to analyze endpoints related to the efficacy objectives and the safety analysis set will be used to analyze the endpoints and assessments related to safety.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

Example 2:

The following analysis data sets are defined to estimate the estimands defined in the protocol and to address safety.

|  |  |
| --- | --- |
| **Analysis Data Sets** | **Description** |
| Analysis data set 1:  for the primary estimand and for the secondary estimand for the secondary objective 1 | PAS1: All randomized participants.  All data points obtained at or after randomization up to the earliest date of discontinuation of investigational intervention or administration of rescue therapy. |
| Analysis data set 2:  for the supplementary estimand for the primary objective | PAS1  All data points obtained at or after randomization up to the [end of study] visit. |
| Analysis data set 3:  for safety assessments with a long lag-time | PAS2: All participants who are exposed to investigational intervention.  All observed data. |
| Analysis data set 4:  for safety assessments with an acute onset | PAS2  All data points obtained at or after randomization until discontinuation of investigational intervention. |

PAS : participant analysis set

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

Example 3:

The following participant analysis sets are defined:

| **Participant Analysis Set** | **Description** |
| --- | --- |
| Full analysis set (FAS) | All randomized participants. |
| Safety analysis set (SAS) | All participants who are exposed to investigational intervention. |

**The following data points sets are defined:**

| **Data Points Sets** | **Description** |
| --- | --- |
| DPS1 | All data points obtained at or after randomization up to the earliest date of discontinuation of investigational intervention or administration of rescue therapy. |
| DPS2 | All data points obtained at or after randomization up to the [end of study] visit. |
| DPS3 | All observed data. |
| DPS4 | All data points obtained at or after randomization until discontinuation of investigational intervention. |

DPS: Data Points Set

FAS and DPS1 will be used to estimate the primary estimand and the secondary estimand for secondary objective 1.

FAS and DPS2 will be used to estimate the supplementary estimand for the primary objective.

SAS and DPS3 will be used to present safety data with a long lag-time.

SAS and DPS4 will be used to present safety data with an acute onset.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

<End of example text>

## Analyses Supporting Primary Objective(s)

Add level 3 subsections for the analysis of all endpoints/estimands supporting the primary objective(s), as applicable, after Section 9.3.1.

### Primary [Endpoint(s)/Estimand(s)]

#### Definition of endpoint(s)

* State how the primary endpoint(s) will be defined/calculated/derived and used to address the primary objective, if not clear from Section 3.
* Describe if the primary endpoint will be transformed, such as square-root and logarithm before analysis. It is recommended to include the rationale/justification for transformation and the interpretation.

#### Main Analytical Approach

* Refer to estimand(s) in Section 3 and ICH E9 (R1) if applicable. In case of more than one primary estimand due to different requirements across different regulatory agencies, describe the analysis of the primary endpoint for all primary estimands and indicate which estimands are required by which authorities if this is not clear from Section 3.
* Refer to the analysis set to be used in the main analytical approach(es).
* Refer to the Decision Criteria/Statistical Hypotheses subsection (in Section 9.1 of this template) regarding the hypothesis to be tested, if applicable.
* Describe the main analytical approach(es) (aligned to the primary estimand[s] and with a description of the handling of each type of intercurrent event, (if applicable and not described in Section 9.1). Describe how missing data will be handled, if not described in Section 9.1. In case of multiple imputation, state imputation model, number of datasets, and seed. Specify how datasets will be combined.
* Describe (if applicable) factors, covariates, stratification factors, etc, to be included in the analysis model.
* Describe underlying assumption(s) of the main analytical approach(es) including assumptions on the missing data mechanism.

#### Sensitivity [Analysis/Analyses]

* Describe the planned sensitivity analyses and how the sensitivity analyses will target the assumptions behind the main analytical approach or limitations in data. Pay special attention to assumptions regarding the missing data mechanism. If a range of methods is proposed, each should target different assumptions in order to explore how these may influence the results obtained from the main analysis.

#### Supplementary [Analysis/Analyses]

* Describe any supplementary analyses. This could be estimation of supplementary estimands defined in Section 3 for the primary objective, if it will not be described as a stand-alone estimand in a level 3 subsection. If not described in Section 9.2, describe which participants and data points are included in the analysis set to be used to estimate each of the estimand(s) related to supplementary analyses. Consider if supplementary analyses including estimand definitions related to them can be moved to the SAP.

## Analyses Supporting Secondary Objective(s)

* Add level 3 subsections as required according to the number of secondary objectives.

### Analyses Supporting Secondary Objective [label]

* Key/confirmatory secondary endpoint(s)/estimand(s) (eg, for which a label claim is pursued) are part of the confirmatory hypotheses where the type 1 error is controlled (via multiplicity adjustment). It is recommended to use the same structure as in Section 9.3 and describe the analysis of such endpoint(s)/estimand(s) to the same level of detail as the primary endpoint(s)/estimand(s) being described in Section 9.3.1.2 and Section 9.3.1.3. If the same methodology/analytical approach is taken for these endpoint(s)/estimand(s), it will be sufficient to add a cross-reference to Section 9.3.1.2/9.3.1.3 to avoid redundancy.
* Analysis of other supportive endpoint(s)/supplementary estimand(s) need not be described with the same level of detail as the key secondary endpoint(s)/estimand(s). A description of supportive secondary endpoint(s)/estimand(s) can be omitted from the protocol section with a reference made to the SAP.

## Analyses Supporting [Tertiary/Exploratory/Other] Objective(s)

It is optional if a description will be provided in the protocol section or in the SAP. If the description is provided in the SAP only a reference to the SAP should be made in this section. If the description is provided in the protocol section, it is recommended to describe the analyses to the same level of detail as the supportive secondary endpoint(s)/estimand(s). For example, no sensitivity or supplementary analyses need to be specified for tertiary/exploratory/other endpoints/estimands unless such analyses are planned to be made.

Add subsections as required according to the number of tertiary/exploratory/other objectives.

## [Other] Safety Analyses

* Describe at a high level how the safety data will be analyzed if not already described in either Section 9.3, Section 9.4, or Section 9.5. Refer to the SAP for details.
* Specify the analysis set to be used or refer to Section 9.2.
* Specify estimands, if applicable and not defined in Section 3.

## Other Analyses

A description can be omitted from the protocol section and a reference made to the SAP. Alternatively, a high-level description can be provided and further detailed in the SAP, if not fully detailed in the study protocol.

Analysis of other variables and/or parameters and subgroup analyses belong to this section.

### Other variables and/or parameters

Other analyses may include analyses of assessments or derived parameters, which are not defined as endpoints but need to be prespecified in either the protocol or SAP. Examples include but are not limited to immunogenicity, biomarkers, PK/PD/population PK parameters, health care utilization variables, and health technology assessment-related variables. State if these will be reported in a separate document.

Subsections may be used for different topics.

It is recommended that the variables used in the analyses should be clearly defined and the analyses should be described at the same level of detail as the supportive secondary endpoint(s)/estimand(s).

The definition and derivation may be specified in a table format.

Specify estimands if applicable and not defined in Section 3.

### Subgroup analyses

Note: Often individual standard clinical studies (excluding large outcomes or safety studies) are not designed to allow for statistically meaningful subgroup analyses because of too small sample sizes. Also, subgroup analyses are not commonly included in the set of multiplicity-controlled analyses and are therefore subject to multiplicity issues.

It is recommended to consider addressing the following topics, if applicable:

* Define the endpoints subject to subgroup analysis – can be for either efficacy and safety, or both.
* Define subgroups (may include stratification factor, if relevant). Specify how participants will be classified into a subgroup in case of missing information.
* Provide the purpose (consistency, hypothesis) of each subgroup analysis. The subgroup analyses should preferably be further substantiated, eg, biological plausibility of anticipated differential effect, regulatory/payer requirement.
* Specify any rules to define the minimum size of a subgroup in order to carry out the analysis.
* Specify analysis sets/estimand(s), as applicable.
* Specify the subgroup analysis methods including how missing data are handled.
* Specify the level of significance for the test of the investigational intervention/treatment condition-by-subgroup interaction, if applicable.
* Assess consistency across regions and subpopulation(s) for multiregional clinical studies, as specified in ICH E17.
* Describe how results will be presented. It is recommended to focus on estimates and confidence intervals rather than p-values. It is often useful to display the results in a forest plot.

## Interim [Analysis/Analyses]

If an interim analysis is planned, describe if any type of data monitoring committee will be established to evaluate the interim analyses (the safety data and/or the critical efficacy endpoints) in accordance with ICH E9. Also describe the role of the committee (eg, making recommendation to the sponsor whether to continue, modify, or stop a study). Full details of the committee including any charters should be included in Appendix 10.1.5 Committees Structure.

The following information belongs in this section:

* Reason for conducting interim analyses and the impact on the conduct of the study
* Endpoints to be included in the interim analyses
* Timing of the interim analyses (eg, number of participants enrolled, number of participants completing a certain number of visits, number of events, calendar time)
* Any actions resulting from an interim analysis such as sample size re-estimation or stopping rules
* Multiplicity considerations relating to the interim and final analyses
* Blinding/ unblinding strategy

<Start of example text>

An interim analysis of the primary endpoint will be performed by the independent data monitoring committee (IDMC), consisting of [X] clinicians and 1 statistician who are independent experts not otherwise involved in the study when approximately [X] primary events have occurred. The analysis method for the primary efficacy endpoint described in Section 9.3.2 Primary Endpoints/Estimands will be used for the interim analysis. Based on the group sequential design with the [O’Brien Fleming] alpha spending approach, a 2-sided alpha of [X] will be allocated to the interim analysis. In addition, if the conditional power for the final analysis (based on the original assumption for the remaining study) is [X] or lower, the study may be stopped for futility.

The interim analysis will be conducted such that the ongoing study integrity is maintained. Only the independent statistical support group, who is responsible for providing the interim analysis results to the IDMC will be unblinded to the individual treatment group assignments. Interim analysis results will not be shared with investigators, participants, or the study team who are involved in the conduct of the study before the final database lock.

The statistical analysis plan will describe the planned interim analyses in greater detail.

<End of example text>

## Sample Size Determination

* State the expected number of participants to be screened, enrolled, assigned to investigational intervention, when applicable. Consistent with the estimand chosen (where applicable) state the assumptions for intercurrent events: frequency per treatment condition and the assumed impact these may have on the effect size and variation. For an event‑driven study, state the number of events planned along with the number of participants to be randomized. Adapt the text to the study design.
* When applicable (eg, studies not using an estimand concept), ensure this section clearly explains how non-evaluable participants are defined.
* Provide justification of sample size in accordance with the primary and/or other relevant statistical analysis and study objectives/estimands.
* Assumptions and methodology for calculations (and/or simulations) should be provided with references. If possible, the estimand used in the reference study should be mentioned. The sensitivity to these assumptions should be investigated by presenting different scenarios based on varying assumptions.
* The actual sample size reached in the study will rarely be exactly equal to the target sample size. Therefore, please add the word approximately in the text when stating the target sample size. This ensures that the protocol covers the potential to slightly over- or underenroll.
* Include power calculations and level of significance to be used as appropriate. If applicable, describe adjustments for multiple comparisons and/or considerations as to disjunctive or marginal power depending on the clinical objectives.
* If the sample size is not based on statistical considerations, as outlined above, provide a justification. An alternative to providing a statistical justification for the sample size is to state that the sample size is not based on statistical considerations and then discuss the statistical implications of the chosen sample size.
* As applicable, discuss allocation of participants with respect to region-/country-specific regulatory requirements.
* As applicable, specify the software (and version) used to determine the sample size.

<Start of example text>

Approximately [X] participants will be [enrolled/randomized/assigned to investigational intervention]. The sample size calculation is based on the primary efficacy estimand and its endpoint [X].

It is assumed that the proportion of participants achieving response for [X] is [X]% in the placebo intervention arm and [X]% in the arm receiving [intervention X]. Using the normal approximation method for a 2-sided statistical test as described in Section 9.3.2, a study with an overall sample size of N =[X] participants will have over 90% power to detect a treatment difference between the two investigational interventions at a type-1 error level of 5%.

In addition, this sample size will provide [X]% power to demonstrate a difference between arm [X] and arm [X] for endpoint [X] (statistical test related to estimand [X]), under the assumptions [X, Y, Z …].

The additional assumptions for the power calculation relating to intercurrent events are as follows [X, Y, Z].

<End of example text>

# Supporting Documentation and Operational Considerations

Information that is too lengthy and could detract from the reader’s comprehension if included in the body of the protocol should be included in an appendix.

The order of the sections is determined by the order in which they are first referenced in the protocol text.

Modify, delete, or add sections as needed.

## Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

<Start of common text>

### Regulatory and Ethical Considerations

* This study will be conducted in accordance with the protocol and with the following:
  + Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  + Applicable ICH Good Clinical Practice (GCP) guidelines.
  + Applicable laws and regulations.
* The protocol, protocol amendments, ICF, investigator’s brochure, [IDFU], and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before implementation.
* Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
* Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
* The investigator will be responsible for the following, as applicable:
  + Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  + Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  + Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies conducted in the EU, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

<End of common text>

### Financial Disclosure

Include text related to financial disclosure if not included in another document.

<Start of example text>

[Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.]

<End of example text>

### Informed Consent Process

Include the primary ethical concerns of this study. Consider the key elements of the informed consent process, including any special concerns and how addressed (eg, assent, capacity, legally acceptable representative).

<Start of common text>

* The investigator or the investigator’s representative will explain the nature of the study, including the risks and benefits, to the potential participant [or their legally authorized representative [defined as [X]] and answer all questions regarding the study.
* Potential participants must be informed that their participation is voluntary. They [or their legally authorized representatives] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
* The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
* Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
* A copy of the ICF(s) must be provided to the participant [or their legally authorized representative].

<End of common text>

If participants can be rescreened, add the text to state whether the participant needs to sign a new ICF for rescreening.

<Start of example text>

[A participant who is rescreened is not required to sign another ICF if the rescreening occurs within (X) days from the previous ICF signature date.]

OR

[Participants who are rescreened are required to sign a new ICF]

If participants will be asked to consent to optional exploratory research using the remainder of mandatory samples, include text that addresses the use of remaining mandatory samples for optional exploratory research.

[The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant’s agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.]

For studies including participants able to give birth consider including the relevant text.

[If a participant becomes pregnant during the study, the investigator or authorized designee will explain the benefits and risks of continuing or stopping the study intervention to the participant to allow an informed decision based on available data. Pregnant participants who choose to continue should complete an additional ICF specific to the benefit-risk consideration of study intervention exposure during pregnancy.]

For studies conducted under a master protocol, provide details pertaining to any unique consent approaches, for example single vs 2-step consents.

[For complex studies with randomization across sub-protocols, the 2-step consent may be used. Upon having signed the Master ICF, participants will be assigned to a sub-protocol (based on data registered into the IWRS) for which they will sign the corresponding sub-protocol ICF. This process will avoid participants being allocated to sub-protocols for which they may not qualify.]

<End of example text>

### Recruitment strategy

To comply with the EU-CTR, include a brief description of the recruitment strategy and the tools used (eg. newspaper advertisements).

### Data Protection

Include all measures to be taken to comply with the applicable rules on protection of personal data and any relevant information on measures to be taken in case of a data security breach.

For studies conducted in the EU: To address EU-CTR, consider including the suggested bullets about the sponsor/study-site responsibilities and use of secured information technology systems.

<Start of common text>

* Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
* The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
* The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, [by appropriate IRB/IEC members,] and by inspectors from regulatory authorities.

<End of common text>

<Start of example text>

* The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
* Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

<End of example text>

### Committees Structure

Briefly describe the administrative structure for the study (eg, internal review committee/internal review forum, central laboratories, steering committee, expert advisory committee, data monitoring committee or data safety monitoring board, contract research organization). Note that specific details are not required.

If a data monitoring committee is used, please include a section discussing any procedures relating to its operations (eg, charter, composition and schedule of meetings, etc). Consider the need for a closely monitored setting following initial dosing with the study intervention.

For complex studies, describe here all committee(s) relevant to all sub-protocols, and include the statement, if applicable: “Other committees may be described in the associated sub-protocol(s).”

#### [Early Safety Data Review AND/OR Committee]

Choose from the options provided and modify as required. Enter additional details as appropriate for the study design, eg, dose ranging. If the study does not include an early safety data review then only include the final bullet and delete the preceding ones. This last bullet should be deleted if an early safety data review is part of the study.

<Start of example text>

* Participant safety will be continuously monitored by the [sponsor’s internal or external] [safety review or insert others] committee, which includes safety signal detection at any time during the study.
* In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to [study intervention] administration. An initial safety review for this study is planned for the first [X participants/X% of participants] who are dosed and have provided safety data for [X] days after administration of Dose [X].
* All safety data collected will be summarized and reviewed by the [sponsor’s internal/external safety review or other committee] for agreement of next steps.
* In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a requirement to [pause/stop] the study.
  + [Any deaths, regardless of causality]
  + [Any vaccine-related SAEs]
  + [Grade 3 fever reported in more than 2 participants (see table in Appendix [3/7])]
  + [Other]
* [Enrollment will be paused during the review]. If a [pausing/stopping] rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.
* Case unblinding may be performed for above reviews if necessary.

<End of example text>

### Dissemination of Clinical Study Data

Describe company-specific policy on provision of study results.

If individual study data will be provided to participants, indicate details here.

For studies conducted in the EU under Regulations EU 536/2014: Consider whether submission of results of the clinical trial, together with a summary that is understandable to a layperson, will be delayed from defined timelines after the end of the study and provide substantiated justifications and a specified planned submission date. Provide justification if a single summary of results report will not be submitted for all study interventions used in the clinical study.

Include how the following will be handled.

* Disclosure of CSRs, periodic safety reports, and clinical study summary reports after review by regulatory authorities. This includes access to CSRs from studies with negative outcomes and from terminated development programs.
* The posting of company-sponsored study information and tabular study results on the US National Institutes of Health’s website [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and other publicly accessible sites
* Publication planning and other activities related to nonpromotional, peer-reviewed publications, to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company. The granting of access to analyzable datasets from clinical studies through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party

<Start of example text>

Study participants will be provided the option of receiving their individual study data. Management of dissemination and process for providing this option may be found in the study data management or individual participant data return plan in accordance with sponsor policies, laws, and regulations.

<End of example text>

### Data Quality Assurance

<Start of common text>

* All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
* Guidance on completion of CRFs will be provided in [specify location of information].
* The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
* [Quality tolerance limits (QTLs) will be predefined in the [state location(s)] to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.]
* Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the [monitoring plan] [contracts].
* The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
* The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
* Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for [X] years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

<End of common text>

### Source Documents

<Start of common text>

Describe procedures for the identification of data to be recorded directly on the CRF considered as source data.

* Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
* Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
* Definition of what constitutes source data and its origin can be found in [eg, source data acknowledgment or monitoring guidelines].
* The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
* The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

<End of common text>

### Study and Site Start and Closure

**First Act of Recruitment**

<Start of example text>

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the [first site open] OR [insert other] and will be the study start date.

<End of example text>

**Study/Site Termination**

<Start of common text>

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

* Discontinuation of further study intervention development

For site termination:

* Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor’s procedures, or GCP guidelines
* Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
* Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

<End of common text>

### Publication Policy

The following information is required by ICH to be in the protocol if not addressed in another document. If addressed in site contracts, this section can be deleted.

<Start of common text>

* The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
* The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
* Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

<End of common text>

## Appendix 2: Clinical Laboratory Tests

* An example table is provided for listing laboratory tests. Modify as required for the study.
* Consider adding Level 3 headings for laboratory assessments for safety, and immunogenicity or biomarkers if relevant.
* Abbreviations appearing in these tables do not need to be repeated in the abbreviations list.
* If any of the tests are for screening purposes only, please specify.
* Indicate if the participants must be fasting (length of time) or nonfasting.

Procedure Notes

* Hepatitis B and Hepatitis C screening:
  + For Phase 1 and Phase 2 studies, hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV antibody) testing may be required. For potent immunosuppressive agents, participants should also undergo testing for hepatitis B core antibody (HBcAb).
  + For Phase 3 studies, hepatitis testing may not be required unless immunosuppressive agents will be administered. Refer to exclusion criteria for additional guidance.
* For complex studies, include all laboratory tests that are applicable to all sub-protocols in the master protocol. Laboratory tests that are applicable to an individual intervention or population should be described in the applicable sub-protocol(s).

<Start of common text>

* The tests detailed in Table [X] will be performed [by the central laboratory] [by the local laboratory].
* [Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.]
* [Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.]
* Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

<End of common text>

<Start of example text>

Table X: Protocol-required Safety Laboratory Tests

|  |  |  |
| --- | --- | --- |
| Laboratory Tests | Parameters | |
| Hematology | Platelet count | |
| Red blood cell (RBC) count | |
| RBC indices | Mean corpuscular volume (MCV)  Mean corpuscular hemoglobin (MCH)  %Reticulocytes |
| White blood cell (WBC) count with differential: | Neutrophils  Lymphocytes  Monocytes  Eosinophils  Basophils |
| Hemoglobin | |
| Hematocrit | |
| Clinical chemistry1 | Blood urea nitrogen (BUN)  Potassium  Creatinine  Sodium  Calcium  Glucose [indicate if fasting or nonfasting] | Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT)  Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)  Alkaline phosphatase2  Total and direct bilirubin  Total protein |
| Routine urinalysis | Specific gravity  pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick  Microscopic examination (if blood or protein is abnormal) | |
| Pregnancy testing | Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for CBP participants as defined in Patient/Healthy Volunteer libraries Appendix 4.)3 | |
| Other screening tests | Follicle-stimulating hormone and estradiol (as needed in NCBP participants only as defined in Patient/Healthy Volunteer libraries Appendix 4.)  [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)]  [Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] [or specify other tests] [if applicable]  If a central laboratory is being used and protocol-required additional local tests are needed, include the last bullet in the Other screening tests section of the table ([All study required laboratory…)  [All study-required laboratory tests will be performed by a central laboratory, with the exception of [list the exceptions]:  [SPECIFY REQUIRED TEST(S)] | |
| NOTES:  Details of liver chemistry stopping criteria and required actions and follow-up are given in Section [7.1.1 Liver Event Stopping Criteria] and Appendix [6: Liver Safety: Suggestions and Guidelines for Liver Events.]. All events of ALT [or AST] ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT [or AST] ≥3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy’s law), must be reported to [sponsor] in an expedited manner (excluding studies of hepatic impairment or cirrhosis).  If alkaline phosphatase is elevated, consider fractionating.  Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC | | |

<End of example text>

<Start of common text>

Investigators must document their review of each laboratory safety report.

<End of common text>

## Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Note: For medical device studies use ISO definitions and procedures detailed in Appendix 7 AEs, ADEs, SAEs, SADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow‑up, and Reporting in Medical Device Studies]. Insert cross-reference here to Appendix 7, mark this appendix as not applicable, and delete text provided.

**For combination products, or when the study intervention is delivered by a device,** it is recommended that both Appendix 3 and Appendix 7 are included in the protocol to meet regulatory reporting requirements.

The definitions and procedures in Appendix 3 should be used for AEs and SAEs which do **not** involve sponsor-provided medical devices used in this study (see Section 6.1.1 for the list of sponsor medical devices). For events during the study that **do** involve the device, refer to Appendix 7 for definitions and reporting requirements for medical device AEs, SAEs, incidents, and deficiencies.

<Start of common text>

### Definition of AE

**AE Definition**

* An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
* NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Add these definitions of unsolicited and solicited AEs to Appendix 3 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting] at the end of Section 10.3.1 if relevant, eg, for vaccine and pediatric studies.

**Definition of Unsolicited and Solicited AE**

* An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a [participant/participant’s parent(s)/legally authorized representative (LAR)(s)] who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
* Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The [participants/participant’s parent(s)/LAR(s)] will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of [participant/participant’s parent(s)/LAR(s)] concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant’s records.
* Unsolicited AEs that are not medically attended nor perceived as a concern by the [participant/participant’s parent(s)/LAR(s)] will be collected during an interview with the [participants/participant’s parent(s)/LAR(s)] and by review of available medical records at the next visit.
* Solicited AEs are predefined local [at the injection site] and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

**Events Meeting the AE Definition**

For efficacy studies, include the penultimate bullet, and for nonefficacy studies involving marketed products in established indications, include the final bullet.

* Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant’s condition)
* Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
* New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
* Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
* Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
* [Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.]
* [The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.]

**Events not Meeting the AE Definition**

* Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
* The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
* Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
* Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
* Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

1. **Results in death**
2. **Is life threatening**

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

1. **Requires inpatient hospitalization or prolongation of existing hospitalization**

* In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
* Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

1. **Results in persistent or significant disability/incapacity**

* The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
* This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

1. **Is a congenital anomaly/birth defect**
2. **[Is a suspected transmission of any infectious agent via an authorized medicinal product]**
3. **Other situations:**

* Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  + Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

Add other SAEs relevant per protocol/study intervention. Obtain agreement with the pharmacovigilance group on any protocol or project-specific SAEs. Such SAEs should be specified in the other situations part of the SAE definition.

Examples include:

* Grade 4 laboratory abnormalities
* [specify event] – see Section [X] for definition
* [specify event] leading to permanent discontinuation of study intervention

### Recording and Follow-Up of AE and/or SAE

**AE and SAE Recording**

* When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
* The investigator will then record all relevant AE/SAE information.
* It is **not** acceptable for the investigator to send photocopies of the participant’s medical records to [X] in lieu of completion of the [X]/required form.
* There may be instances when copies of medical records for certain cases are requested by [X]. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to [X].
* The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

* Mild:  
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
* Moderate:   
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
* Severe:   
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Other measures to evaluate AEs and SAEs may be used (eg, National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

**Assessment of Causality**

* The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
* A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
* Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
* For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
* The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to [X]. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to [X].
* The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
* The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

* The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [X] to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
* [If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide [X] with a copy of any postmortem findings including histopathology.]

Suggested bullet in variable blue text may not be required for studies where death is an endpoint.

* New or updated information will be recorded in the originally submitted documents.
* The investigator will submit any updated SAE data to [X] within 24 hours of receipt of the information.

### Reporting of SAEs

**SAE Reporting to [X] via an Electronic Data Collection Tool**

* The primary mechanism for reporting an SAE to [X] will be the electronic data collection tool.
* If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
* The site will enter the SAE data into the electronic system as soon as it becomes available.
* After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
* If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the [X/medical monitor/SAE coordinator] by telephone.
* Contacts for SAE reporting can be found in [X].

**SAE Reporting to [X] via Paper Data Collection Tool**

* [Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the [X/medical monitor or the SAE coordinator].
* [In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.]
* Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
* Contacts for SAE reporting can be found in [X].

<End of common text>

## Appendix 4: Contraceptive and Barrier Guidance

Delete appendix if not required.

Insert content for this appendix from the participant libraries as appropriate based upon the decision trees in Section 5.1.

<Start of common text>

### Definitions

See participant libraries for common text to include here.

### Contraception Guidance

See participant libraries for common text to include here.

<End of common text>

## Appendix 5: Genetics

Delete appendix if not required.

For complex studies with different interventions, include any intervention-specific or population-specific guidance in the applicable sub-protocol(s).

<Start of example text>

Use/Analysis of DNA

* Genetic variation may impact a participant’s response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a [blood/saliva] sample will be collected for DNA analysis from consenting participants.
* DNA samples will be used for research related to [study intervention] or [indication] and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to [study intervention and/or interventions of this drug class] and [indication]. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).
* [DNA samples will be analyzed for [describe planned analyses]. [Additional] analyses may be conducted if it is hypothesized that this may help further understand the clinical data.]
* The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to [study intervention] or study interventions of this class to understand the study disease or related conditions.
* The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
* The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
* The samples will be retained while research on [study intervention or study interventions of this class or indication] continues but no longer than [X] years or other period as per local requirements.

<End of example text>

## Appendix 6: Liver Safety: Suggestions and Guidelines for Liver Events

Delete appendix if not required.

See participant libraries for suggested common text.

For complex studies with different interventions, include any intervention-specific guidance in the applicable sub-protocol.

## Appendix 7: Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

Delete appendix if not required.

This appendix is required for a study in which a sponsor medical device is provided for use in the study (ie, there are medical devices listed in Section 6.1.1 that are manufactured by the sponsor or by a third party for the sponsor). If Section 6.1.1 includes only nonsponsor medical devices or is not applicable, then this appendix is not needed.

<Start of common text>

* The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
* Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
* The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

### Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

* A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
* An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

### Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

1. Led to death
2. Led to serious deterioration in the health of the participant, that either resulted in:

* A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
* A permanent impairment of a body structure or a body function.
* Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
* Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
* Chronic disease (MDR 2017/745).

1. Led to fetal distress, fetal death, or a congenital abnormality or birth defect
2. [Is a suspected transmission of any infectious agent via a medicinal product]

SADE definition

* An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.
* Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

* An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

### Definition of Device Deficiency

* A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

### Recording and Follow-Up of Medical Device AE and/or SAE and Device Deficiencies

**Medical Device AE, SAE, and Device Deficiency Recording**

* When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
* The investigator will then record all relevant AE/SAE/device deficiency information in the participant’s medical records, in accordance with the investigator’s normal clinical practice and on the appropriate form.
* It is **not** acceptable for the investigator to send photocopies of the participant’s medical records to [X] in lieu of completion of the [X]/AE/SAE/device deficiency form.
* There may be instances when copies of medical records for certain cases are requested by [X]. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to [X].
* The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
* For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  + A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

* Mild:   
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
* Moderate:   
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
* Severe:   
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Other measures to evaluate AEs and SAEs may be used (eg, National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

**Assessment of Causality**

* The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.
* A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
* Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
* The investigator will also consult the [investigator’s brochure (IB) and/or IDFU or product information, for marketed products] as part of the assessment.
* The investigator must review and provide an assessment of causality for each AE/SAE/device deficiency and document this in the medical notes.
* There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to [X]. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to [X].
* The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
* The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of Medical Device AE/SAE and device deficiency**

* The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [X] to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
* [If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide [X] with a copy of any post‑mortem findings including histopathology.]
* Suggested bullet in variable blue text may not be required for studies where death is an endpoint.
* New or updated information will be recorded in the originally completed form.
* The investigator will submit any updated SAE data to [X] within 24 hours of receipt of the information.

### Reporting of Medical Device SAEs

**Medical Device SAE Reporting to [X] via an Electronic Data Collection Tool**

* The primary mechanism for reporting an SAE to [X] will be the electronic data collection tool.
* If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
* The site will enter the SAE data into the electronic system as soon as it becomes available.
* After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
* If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the [X/medical monitor/SAE coordinator] by telephone.
* Contacts for SAE reporting can be found in [X].

**Medical Device SAE Reporting to [X] via Paper Data Collection Tool**

* [Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the [X/medical monitor/SAE coordinator]].
* [In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.]
* Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
* Contacts for SAE reporting can be found in [X].

### Reporting of SADEs

SADE Reporting to [X]

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

* Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
* The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
* Contacts for SAE reporting can be found in [X].

<End of common text>

## Appendix 8: Country-specific Requirements

Delete appendix if not required.

Do not use this appendix to create extensive lists of country-specific differences. Protocol requirements and specifications outlined in the body of the protocol should be authored using flexible language to accommodate local variation where permissible and within the parameters of the study design; this appendix should be used for requirements that cannot be addressed by flexible language.

Discuss with local regulatory groups whether country specific requirements need to be included in the appendix. The country-specific appendix may include a list (by country) of country-specific requirements in order that any requirements for a given country can be seen in one location.

Country-specific requirements listed in the appendix should also be clearly cross-referenced within the body of the document, within the sections they refer to, but details should not be included.

Countries where contraception requirements may differ: Australia, Japan

Korea: Local sponsor should be identified in addition to company sponsor on protocol agreement page.

For country/region-specific pregnancy & breastfeeding-related requirements as of May 2022 please see the Initiatives & Regulatory Landscape Assessment Output.

## Appendix 9: Protocol Amendment History

Delete appendix if not required.

Example text is included in this appendix for the Protocol Amendment History located here and the Protocol Amendment Summary of Changes Table located before the table of contents.

<Start of common text>

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

See the instructions in the Protocol Amendment Summary of Changes Table located before the table of contents. Move all Protocol Amendment Summary of Changes Tables for previous amendments to this appendix.

Amendment [amendment number]: ([date])

This amendment is considered to be [substantial/nonsubstantial] based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament.

**Overall Rationale for the Amendment**

[Rationale]

|  |  |  |
| --- | --- | --- |
| Section # and Name | Description of Change | Brief Rationale |
|  |  |  |
|  |  |  |
|  |  |  |

<End of common text>

<Start of example text>

**Amendment 3: 30 March 2016**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**Overall Rationale for the Amendment**

Current literature supports use of this class of interventions in a higher age range for this patient population.

|  |  |  |
| --- | --- | --- |
| **Section # and Name** | **Description of Change** | **Brief Rationale** |
| 5.1. Inclusion Criteria | Removed maximum age range | To better reflect the age of the patient population |
| Throughout | Minor editorial and document formatting revisions | Minor, therefore have not been summarized |

Example of Numbering Global and Country-specific Protocol Amendments

|  |  |  |
| --- | --- | --- |
| Type of Protocol Amendment | Numbering | Type of changes |
| Country-specific | Amendment 3/FRA-2 | Same changes specific to France added to global Amendment 3 (no new changes for France) |
| Global | Amendment 3 | New changes for all |
| Country-specific | Amendment 2/FRA-2 | Additional changes specific to France added to global Amendment 2 |
| Country-specific | Amendment 2/FRA-1 | Same changes specific to France added to global Amendment 2 (no new changes for France) |
| Global | Amendment 2 | New changes for all |
| Country-specific | Amendment 1/FRA-1 | Same changes specific to France added to global Amendment 1 (no new changes for France) |
| Global | Amendment 1 | New changes for all |
| Country-specific | Amendment FRA-1 | Changes specific to France added to original protocol |

Example of Numbering a Site-specific Protocol Amendment

|  |  |  |
| --- | --- | --- |
| Type of Protocol Amendment | Numbering | Type of changes |
| Site-specific | Amendment 2/SS-1 <<Insert Site Number(s)>> | Same changes specific to site(s) added to global Amendment 2 (no new changes for site[s]) |
| Global | Amendment 2 | New changes for all |
| Site-specific | Amendment 1/SS-1 <<Insert Site Number(s)>> | Changes specific to site(s) added to global amendment |
| Global | Amendment 1 | New changes for all |

Example of Document History Table for Global and Country-specific Protocol Amendments

|  |  |
| --- | --- |
| DOCUMENT HISTORY | |
| Document | Date of Issue |
| Amendment 2/FRA-1 | 1-Feb-2016 |
| Amendment 2 | 1-Feb-2016 |
| Amendment 1/FRA-1 | 1-Jan-2015 |
| Amendment 1 | 01-Dec-2015 |
| Original Protocol | 01-Oct-2015 |

Example of Document History Table for Site-specific Amendments to a Global Amendment

|  |  |
| --- | --- |
| DOCUMENT HISTORY | |
| Document | Date of Issue |
| Amendment 2/SS-1 | 1-Feb-2016 |
| Amendment 2 | 1-Feb-2016 |
| Amendment 1/SS-1 | 1-Jan-2015 |
| Amendment 1 | 01-Dec-2015 |
| Original Protocol | 01-Oct-2015 |

<End of example text>

# References

* See therapeutic libraries for key references to include.
* References to both internal and external documents and publications should be listed in alphabetical order. Do not reference internal reports in preparation.
* In the reference list, use the style and format published by the International Committee of Medical Journal Editors (ICMJE 2019). Citations to external documents and publications should be indicated in the text by citing the author and year within parentheses. For example, the in-text citation for the reference included would be (Hatcher et al, 2007).

<Start of example text>

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, eds. Contraceptive technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.

<End of example text>