**Common Protocol Template v4.0**

**About This Template**

**Disclaimer**

This document is a common protocol template. It contains sections marked as common text or 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.

These materials are provided 'AS IS' WITHOUT WARRANTY OF ANY KIND, EITHER EXPRESSED OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT. TransCelerate and its members do not accept any responsibility for any loss of any kind including loss of revenue, business, anticipated savings or profits, loss of goodwill or data, or for any indirect consequential loss whatsoever to any person using these materials or acting or refraining from action as a result of the information contained in these materials. Any party using these materials bears sole and complete responsibility for ensuring that the materials, whether modified or not, are suitable for the particular use and are accurate, current, commercially reasonable under the circumstances, and comply with all applicable laws and regulations.

Nothing in this template should be construed to represent or warrant that persons using this template have complied with all applicable laws and regulations. All individuals and organizations using this template bear responsibility for complying with the applicable laws and regulations for the relevant jurisdiction.

**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 TransCelerate Common Protocol Template (CPT) for reference and mapping purposes.
* 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 lower headings can be deleted/added/modified as needed with the exception of those in Section 8.3 relating to Adverse Events which are International Council on Harmonisation (ICH)/Regulatory Agency required wording and must be included.

**Terminology**

* The following terminology has been selected for use within this template and is considered to be appropriate for all phases, study populations, and therapeutic areas.
  + *Participant* is used rather than subject, healthy volunteer, or patient.
  + *Study intervention* is used rather than study drug. Study intervention covers all types of investigational and non-investigational products including medical devices and vaccines.
    - Study intervention is defined as investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per protocol.

**Formatting and Text Conventions**

* Common Headings: Heading levels 1 and 2 should not be altered or deleted (indicate “not applicable” if needed).
* Suggested Headings: Heading levels 3 and lower are suggested and may be modified as necessary.
* 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 if required. The flags for the start and end of common text can be removed automatically at the time of protocol finalization if the technology enabled CPT has been used or should be removed manually by the author
* Suggested Text: Black text that is not flagged as common text is suggested language to be used in optional sections and can be deleted as needed.
* Variable Text: Blue bracketed text is variable text that should be addressed based on individual study needs.
* Example Text: Green italicized text is example text and should be removed by the author.
* 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. In the Technology Enabled Edition, it will appear only in the Instructional Text panel.

Title Page

Protocol Title:

Protocol Title: The protocol should have a descriptive title that identifies the study design including type of blinding, study population, study intervention, and, if applicable, study intervention acronyms. The title should be similar to the Official Study Title in the Clinical Trials (CT) Registry disclosure guidance.

Protocol Number:   
Amendment Number: [amendment number]

Compound Number:

Short Title:

Short title should be sufficiently detailed to make clear to a lay reader what the study is about and preferably suitable for use as the Brief Title in ClinicalTrials.gov and for use with informed consents and ethics committee submissions. It should be limited to 300 characters.

Sponsor Name:

Legal Registered Address:

The sponsor name and legal registered address must be included. 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.

Regulatory Agency Identifying Number(s):

Include all numbers that are applicable for the study and available at the time of protocol finalization eg, Investigational New Drug (IND) number, World Health Organization (WHO) universal trial number, European Clinical Trials Database (EudraCT) number, ClinicalTrials.gov, etc.

**Approval Date:**

Sponsor Signatory:

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

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

Investigator Agreement Page is provided as a stand-alone document. The investigator should retain the original in the site study files and return a copy to the sponsor for archiving.

This page is generated internally and provided alongside the protocol template.

Each investigator should be sent a copy of it for completion. Signatures are obtained after sponsor has finalized and approved the protocol

Protocol Amendment Summary of Changes Table

**Delete this section if this 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/non-substantial amendment status) to ensure alignment with their internal processes and systems.

Protocols should be amended by making the changes directly within the protocol.

**GENERAL INSTRUCTIONS:**

* 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 10, 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 for the previous amendment(s) should be moved to Appendix 10, 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.
* Track changes versions of the current amendment compared to the previous version may be created and provided to the health authorities, etc. as needed.

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

Use International Organization for Standardization (ISO)-Alpha 3 Codes from United Nations Statistics Department for 3-letter codes to represent country or area name in country-specific amendments: http://unstats.un.org/unsd/methods/m49/m49alpha.htm

Examples can be found in Appendix 10, 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 2nd 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.

Examples can be found in Appendix 10, 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 not list country-specific amendments unless they are 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 from ISO-Alpha 3 Codes from United Nations Statistics Department as noted above)
  + Region 2 (list country/area codes from ISO-Alpha 3 Codes from United Nations Statistics Department as noted above)
  + Site-specific SS-1 (Sites 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 10, Protocol Amendment History.

<Start of common text>

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

|  |  |
| --- | --- |
| **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)

Include the following statement if this amendment will be implemented in any European Union (EU) Member State.

This amendment is considered to be [substantial] [nonsubstantial] 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 [because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study].

Include the last phrase for non-substantial amendments only.

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 below (eg, changes to individual inclusion/exclusion criteria). See Appendix 10, 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>

Table of Contents

[1. Protocol Summary 11](#_Toc480358548)

[1.1. Synopsis 11](#_Toc480358549)

[1.2. Schema 11](#_Toc480358550)

[1.3. Schedule of Activities (SoA) 12](#_Toc480358551)

[2. Introduction 14](#_Toc480358552)

[2.1. Study Rationale 14](#_Toc480358553)

[2.2. Background 14](#_Toc480358554)

[2.3. Benefit/Risk Assessment 14](#_Toc480358555)

[3. Objectives and Endpoints 15](#_Toc480358556)

[4. Study Design 16](#_Toc480358557)

[4.1. Overall Design 16](#_Toc480358558)

[4.2. Scientific Rationale for Study Design 16](#_Toc480358559)

[4.3. Justification for Dose 16](#_Toc480358560)

[4.4. End of Study Definition 16](#_Toc480358561)

[5. Study Population 17](#_Toc480358562)

[5.1. Inclusion Criteria 17](#_Toc480358563)

[5.2. Exclusion Criteria 18](#_Toc480358564)

[5.3. Lifestyle Considerations 18](#_Toc480358565)

[5.3.1. Meals and Dietary Restrictions 18](#_Toc480358566)

[5.3.2. 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. Caffeine, Alcohol, and Tobacco 19](#_Toc480358567)

[5.3.3. Activity 19](#_Toc480358568)

[5.4. Screen Failures 19](#_Toc480358569)

[6. Study Intervention 20](#_Toc480358570)

[6.1. Study Intervention(s) Administered 20](#_Toc480358571)

[6.1.1. Medical Devices 21](#_Toc480358572)

[6.2. Preparation/Handling/Storage/Accountability 21](#_Toc480358573)

[6.3. Measures to Minimize Bias: Randomization and Blinding 21](#_Toc480358574)

[6.4. Study Intervention Compliance 23](#_Toc480358575)

[6.5. Concomitant Therapy 23](#_Toc480358576)

[6.5.1. Rescue Medicine 24](#_Toc480358577)

[6.6. Dose Modification 24](#_Toc480358578)

[6.7. Intervention after the End of the Study 25](#_Toc480358579)

[7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 26](#_Toc480358580)

[7.1. Discontinuation of Study Intervention 26](#_Toc480358581)

[7.1.1. Temporary Discontinuation 26](#_Toc480358582)

[7.1.2. Rechallenge 26](#_Toc480358583)

[7.2. Participant Discontinuation/Withdrawal from the Study 26](#_Toc480358584)

[7.3. Lost to Follow Up 27](#_Toc480358585)

[8. Study Assessments and Procedures 28](#_Toc480358586)

[8.1. Efficacy Assessments 28](#_Toc480358587)

[8.2. Safety Assessments 28](#_Toc480358588)

[8.2.1. Physical Examinations 28](#_Toc480358589)

[8.2.2. Vital Signs 29](#_Toc480358590)

[8.2.3. Electrocardiograms 29](#_Toc480358591)

[8.2.4. Clinical Safety Laboratory Assessments 29](#_Toc480358592)

[8.2.5. Suicidal Risk Monitoring 30](#_Toc480358593)

[8.3. Adverse Events and Serious Adverse Events 31](#_Toc480358594)

[8.3.1. Time Period and Frequency for Collecting AE and SAE Information 31](#_Toc480358595)

[8.3.2. Method of Detecting AEs and SAEs 32](#_Toc480358596)

[8.3.3. Follow-up of AEs and SAEs 32](#_Toc480358597)

[8.3.4. Regulatory Reporting Requirements for SAEs 32](#_Toc480358598)

[8.3.5. Pregnancy 32](#_Toc480358599)

[8.3.6. Cardiovascular and Death Events 33](#_Toc480358600)

[8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 33](#_Toc480358601)

[8.3.8. Medical Device Incidents (Including Malfunctions) 33](#_Toc480358602)

[8.4. Treatment of Overdose 34](#_Toc480358603)

[8.5. Pharmacokinetics 35](#_Toc480358604)

[8.6. Pharmacodynamics 35](#_Toc480358605)

[8.7. [Genetics] 36](#_Toc480358606)

[8.8. Biomarkers 36](#_Toc480358607)

[8.8.1. Immunogenicity Assessments [If applicable] 37](#_Toc480358608)

[8.8.2. RNA Transcriptome Research [If applicable] 37](#_Toc480358609)

[8.8.3. RNA Expression Research of a Subset of RNA Species [If applicable] 37](#_Toc480358610)

[8.8.4. Proteome Research [If applicable] 38](#_Toc480358611)

[8.8.5. Metabolomic Research [If applicable] 38](#_Toc480358612)

[8.9. [Health Economics] OR [Medical Resource Utilization and Health Economics] 38](#_Toc480358613)

[9. Statistical Considerations 39](#_Toc480358614)

[9.1. Statistical Hypotheses 39](#_Toc480358615)

[9.2. Sample Size Determination 39](#_Toc480358616)

[9.3. Populations for Analyses 39](#_Toc480358617)

[9.4. Statistical Analyses 39](#_Toc480358618)

[9.4.1. Efficacy Analyses 39](#_Toc480358619)

[9.4.2. Safety Analyses 40](#_Toc480358620)

[9.4.3. Other Analyses 40](#_Toc480358621)

[9.5. Interim Analyses 40](#_Toc480358622)

[9.5.1. Data Monitoring Committee (DMC) 40](#_Toc480358623)

[10. Supporting Documentation and Operational Considerations 41](#_Toc480358624)

[10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 41](#_Toc480358625)

[10.1.1. Regulatory and Ethical Considerations 41](#_Toc480358626)

[10.1.2. Financial Disclosure 41](#_Toc480358627)

[10.1.3. Informed Consent Process 42](#_Toc480358628)

[10.1.4. Data Protection 42](#_Toc480358629)

[10.1.5. Committees Structure 43](#_Toc480358630)

[10.1.6. Dissemination of Clinical Study Data 43](#_Toc480358631)

[10.1.7. Data Quality Assurance 43](#_Toc480358632)

[10.1.8. Source Documents 43](#_Toc480358633)

[10.1.9. Study and Site Closure 44](#_Toc480358634)

[10.1.10. Publication Policy 44](#_Toc480358635)

[10.2. Appendix 2: Clinical Laboratory Tests 45](#_Toc480358636)

[10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 48](#_Toc480358637)

[10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information 54](#_Toc480358638)

[10.5. Appendix 5: Genetics 58](#_Toc480358639)

[10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines] 59](#_Toc480358640)

[10.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting 60](#_Toc480358641)

[10.8. Appendix 8: Country-specific Requirements 62](#_Toc480358642)

[10.9. Appendix 9: Abbreviations 63](#_Toc480358643)

[10.10. Appendix 10: Protocol Amendment History 64](#_Toc480358644)

[11. References 67](#_Toc480358645)

# 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 (CTA) and for other external bodies such as Institutional Review Boards [IRB]/Independent Ethics Committees [IEC]). Its level of detail should not dissuade/discourage the investigator from referring to the main text of the protocol.

Protocol Title:

Short Title:

Rationale:

Briefly (1 paragraph) describe the study rationale and purpose. The synopsis text should be taken from the main text

Objectives and Endpoints

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

Endpoints: This should be a high-level description

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

Overall Design:

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]).
* 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).
* 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.
* Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group

Number of Participants:

* State the expected number of participants to be randomized. If an event driven trial, state the number of events planned along with the number of participants randomized.
* Ensure *evaluable* is clearly defined and cross reference Section 9 Statistical Considerations, if applicable.
* Cross reference Section 9.2 Sample Size Determination and ensure that section clearly explains how screening failures and non-evaluable participants are defined.

Approximately X participants will be screened to achieve X randomly assigned to study intervention and X evaluable participants for an estimated total of X evaluable participants per intervention group.

A maximum of X participants will be randomly assigned to study intervention such that approximately Y evaluable participants complete the study.

Intervention Groups 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
* Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group

Data Monitoring Committee: [Yes/No]

## 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 collection of efficacy or safety data. The acceptable windows can be indicated on the SoA by adding ± days to the Visit Day 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 time point.
* Combine assessments on consecutive weeks if they are identical and consider separate tables for separate phases 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

| Procedure | Screening  (up to X days before Day 1) | Intervention Period [Days or Weeks, etc.] | | | | | | | | | Follow-up  (X days after last dose) | Notes |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| –1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |
| Inclusion and exclusion criteria | X |  |  |  |  |  |  |  |  |  |  | [Recheck clinical status before randomization and/or 1st dose of study medication.] |
| Demography | X |  |  |  |  |  |  |  |  |  |  |  |
| Full physical examination including height and weight | X |  |  |  |  |  |  |  |  |  |  |  |
| Medical history (includes substance usage [and Family history of premature CV disease]) | X |  |  |  |  |  |  |  |  |  |  | Substances: [drugs, alcohol, tobacco, and caffeine] |
| Past and current medical conditions | X |  |  |  |  |  |  |  |  |  |  |  |
| [Serum OR urine] pregnancy test (WOCBP only) | X |  |  |  |  |  |  |  |  |  |  |  |
| [Hepatitis B and C screening] | X |  |  |  |  |  |  |  |  |  |  |  |
| Laboratory assessments (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 |  |  |  |  |  |  |  |  | [Pre-dose/baseline], ICF for genetic sampling should be added per sponsor process (eg, part of ICF or separate ICF). |
| Study treatment |  |  | X |  |  |  |  |  | X |  |  |  |
| AE review |  | X | 🡨=============================🡪 | | | | | | | |  |  |
| SAE review |  | X | 🡨=============================🡪 | | | | | | | | X |  |
| Concomitant medication review |  | X | 🡨=============================🡪 | | | | | | | | X |  |
| [Study specific assessments (eg, PK, efficacy)] |  |  |  | | | | | | | |  |  |

# Introduction

* Overall, this section should be short (recommend 2 to 3 pages) and may be started with an overview description of the study 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, package insert, and other relevant documents; do not duplicate information available elsewhere.

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 (the aim of the study) and for doing it at this time. For example, include any key issues for the compound which are being addressed (eg, variable exposure addressed with a new formulation or dosing with food).
* 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.

## 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 study 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 study intervention: Include a very brief summary of key preclinical/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 Investigator’s Brochure; a reference to the specific Investigator’s Brochure section is sufficient. When referencing information in the Investigator’s Brochure, 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.

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.

[Study 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 [study intervention name] is provided in the [Investigator’s Brochure/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 Investigator’s Brochure, package insert/prescribing information (if applicable), and Investigational Medicinal Product Dossier (IMPD) (if applicable).
* Consider the known and expected benefits and potential risks of the study 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.
* 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 it provides useful insights for the investigator.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of [study intervention name] may be found in the [Investigator’s Brochure, Participant Information Leaflet, Package Insert, Development Safety Update Report or Summary of Product Characteristics].

# Objectives and Endpoints

* 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 and secondary 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.
* Avoid objectives that use vague terms such as assess or evaluate. Objective text should link to the statistical output (eg, compare, estimate). Consultation or review by a statistician is recommended.
* Ensure that there is an endpoint for each study objective including exploratory objectives, if applicable, and that there are no endpoints without a corresponding objective.
* Keep endpoint information at a high level with details placed in Section 8 : Study Assessments and Procedures and/or Section 9: Statistical Considerations. Describe each endpoint (eg, safety and tolerability as determined by AE reporting, vital signs, and ECG instead of just safety and tolerability) but include the specific methodology that will be used in Section 8.
* Consider whether the desired endpoints will be achievable in case of unexpected findings, technical/equipment issues, or personnel failure.
* Tertiary/exploratory objectives may be added to indicate that other assessments will be made to help future research if taking additional samples for these endpoints; otherwise, reference the statistical analysis plan (SAP) for the list of other assessments. These should be kept to a minimum to focus the study on primary objectives. Note that exploratory objectives will not be listed on the ClinicalTrials.gov website.
* If a patient reported outcome (PRO) measure is included in the study, mention the concept being measured (eg, fatigue) as well as the instrument (eg, the impact of study intervention name on 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 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.
* It is recommended that objectives and endpoints be presented together in a table (see example) to ensure all endpoints are aligned with an objective. The format of the table can be adapted for multiple part studies.

|  |  |
| --- | --- |
| Objectives | Endpoints |
| Primary |  |
|  |  |
| Secondary |  |
|  |  |
| Tertiary/Exploratory |  |
|  |  |

# Study Design

## Overall Design

* Include a brief summary of the study design (eg, placebo-controlled, single or multicenter, participant type, blinding, phase).
* Include intervention groups and duration of study for each participant including duration of treatment period.
* Include study periods.
* Do not include study schema
* Do not include the SoA here.
* Use bullets rather than lengthy text, if possible.
* Describe any provisions for extending the study or entry to roll-over studies (cross reference Section 6.7 Intervention after the End of the Study). Do not duplicate information.
* Include a high level description of the study population (eg, healthy volunteers, patients with acute lung injury).
* Do not put sample size justification here. This is covered in Section 9 Statistical Considerations.
* See therapeutic area libraries for additional guidance for studies in specific therapeutic areas.
* The description of the design of the study, should include the kind of control group to be used, if any, and the methods to be used to minimize bias on the part of subjects, investigators, and analysts.

## 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 Investigator’s Brochure or other documents.

## Justification for Dose

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

## End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including [the last visit] or [the last scheduled procedure shown in the Schedule of Activities].

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.

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 trial globally].

# Study Population

<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 trial should reflect the intended use of the drug. This is particularly relevant for planning multiregional trials 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).

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

**Age**

1. Participant must be [18] to [X] years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

For studies in healthy volunteers, begin with this criterion. State whether rescreening will be allowed and the circumstances under which rescreening can occur (eg, laboratory value range) and cross reference Section 5.4 if appropriate:

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.
* State whether rescreening will be allowed and the circumstances under which rescreening can occur (eg, laboratory value range) and cross reference Section 6.4, if appropriate.
* Check whether additional information associated with the disease area can be found in the therapeutic area libraries.

Weight

Consider whether any restriction on weight or BMI is needed for this study intervention/stage of development and delete if not required.

1. Body weight within [insert range including units] and body mass index (BMI) within the range [Y – Z] kg/m2 (inclusive).

Sex

1. [Enter Male and/or female]

Abstinence/contraceptives: Length of time required for abstinence or use of contraceptives should take into account the reproductive toxicity profile including genotoxicity and teratogenicity, the size of the molecule, and the number of doses.

The common text language, per International Council on Harmonization [ICH] Guideline M3(R2) and Clinical Study Facilitation Group Guidance which supports EU536/2014, should be used for most studies.

<Start of common text>

1. Male participants:

If males with a heterosexual partner who is a woman of childbearing potential (WOCBP) are included and the study intervention has a genotoxic or demonstrated/suspected teratogenic/fetotoxic potential at subtherapeutic systemic exposure levels and relevant systemic exposure may be achieved in the WOCBP partner, include the male contraceptive criteria presented in the template common text.

* A male participant must agree to use contraception as detailed in Appendix 4 of this protocol during the treatment period and for at least [X days/weeks, corresponding to time needed to eliminate study intervention for both genotoxic and teratogenic study interventions ***plus*** an additional 90 days (a spermatogenesis cycle) for study interventions with genotoxic potential] after the last dose of study intervention and refrain from donating sperm during this period.

1. Female participants:

* A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:

1. Not a woman of childbearing potential (WOCBP) as defined in Appendix 4

OR

1. A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least [X days/weeks,(5 terminal half-lives and, for genotoxic products, an additional 30 days], corresponding to time needed to eliminate study intervention plus 30 days for study interventions with genotoxic potential after the last dose of study intervention.

<End of common text>

**Informed** **Consent**

<Start of common text>

1. Capable of giving 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>

## Exclusion Criteria

Exclusion Criteria: See 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. []

**Prior/Concomitant Therapy**

1. []

**Prior/Concurrent Clinical Study Experience**

1. []

**Diagnostic assessments**

1. []

**Other Exclusions**

1. []

## Lifestyle Considerations

1. [ ]
2. [ ]

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

Describe any restrictions during any of the study periods pertaining to lifestyle and/or diet. For example, include a statement about exposure to sunlight for study interventions with photosensitivity potential.

### 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.

1. 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. Caffeine, Alcohol, and Tobacco

* Restrictions are dependent on the known metabolism of the study intervention in order 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.

1. 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.
2. 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.
3. 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.

### Activity

Study-specific restrictions may apply depending on the nature and frequency of assessments (eg, in first in human studies, activity may be further restricted by ensuring participants remain in bed for 4 to 6 hours after dosing).

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).

## Screen Failures

<Start of common text>

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently [randomly 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 Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

<End of common text>

State whether rescreening is permitted. If rescreening is permitted, state the entry criteria/parameters which can be reassessed for individuals who previously failed screening and the time period for repeating procedures/rescreening. Individual inclusion/exclusion criteria may also state whether a repeat procedure is allowed without being considered a rescreen.

Individuals who do not meet the criteria for participation in this study (screen failure) [may/may not] be rescreened. [Rescreened participants should be assigned the same participant number as for the initial screening.]

# Study Intervention

<Start of common text>

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

<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.
* For devices, include details on the set-up and use of the device. A Device User Manual can be included as an Appendix.

The example table should be modified as needed

|  |  |  |  |
| --- | --- | --- | --- |
| **Study Intervention Name:** |  |  |  |
| **Dosage formulation:** |  |  |  |
| **Unit dose strength(s)/Dosage level(s):** |  |  |  |
| **Route of Administration** |  |  |  |
| **Dosing instructions:** | [number of tablets to be taken, when and any specific restrictions (eg, to take with or without food)] |  |  |
| Packaging and Labeling  Do not include a sample of the label text or details of pack design in the protocol. | Study Intervention will be provided in [container]. Each [container] will be labeled as required per country requirement. |  |  |
| **Manufacturer** |  |  |  |
| [Device:]  Only use this when a medical device is used. If not applicable, delete row. May also cross reference the Device User Manual in Appendix [X] if provided. |  |  |  |

### Medical Devices

* This section is optional and should be removed if not applicable. A Device User Manual can be included as an appendix to the protocol.
* Describe any sponsor provided medical devices for use in the study.
* **Consult with Regulatory Affairs within sponsor** if use of a device is required for the study as not all devices are defined as medical devices and different regions have different definitions of a medical device.
* Examples of sponsor medical devices include, but are not limited to, the following: metered dose inhaler, auto‑injector, inhalation spacers, measuring cups, measuring spoons, pediatric oral syringes, and dry‑powder inhalers.
* Include details of the preparation and use of the device in the protocol or a Device User Manual
* The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.

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. XX medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study. (see Section 8.3.8).

## Preparation/Handling/Storage/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.

<Start of common text>

1. The investigator or designee must confirm appropriate temperature conditions 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 enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. 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.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. 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>

## Measures to Minimize Bias: Randomization and Blinding

* 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 treatment 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.
* State any other study/project-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.

Example text:

|  |  |
| --- | --- |
| **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 & directions for the IWRS will be provided to each site.  Study intervention will be dispensed at the study visits summarized in SoA.  Returned study intervention should not be re-dispensed to the participants. |
| **Study using Pre‑Coded 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 his/her unique randomization number, throughout the study. |

End of example text

* “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 (for example, studies involving visually-impaired participants), but maintain consistent usage within the protocol.
* Single-blind refers to studies in which participants are blinded to study intervention, but site personnel (for example, 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 (for example, the site pharmacist or the sponsor’s clinical trial material group), describe the means 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 SAE), the procedures to be used to do this, and who has access to participant codes. If the study allows for some investigators to remain unblinded (eg, to allow them to adjust medication), the means of shielding other investigators should be explained.

Example text:

|  |  |
| --- | --- |
| **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)** | 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’s treatment 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 should make every effort to contact the sponsor prior to unblinding a participant’s treatment assignment unless this could delay emergency treatment of the participant. If a participant’s treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. |
| **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**: This is not an approach to be supported from a statistical perspective. Open-label randomized trials need to use central randomization. If envelopes are pre-assigned 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)** | 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 participants’s treatment 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 should make every effort to contact the sponsor prior to unblinding a participant’s treatment assignment unless this could delay emergency treatment of the participant. If a participant’s treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the sponsor. |
| **Blinded study with unblinded site pharmacist who is dispensing drug** | 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. In order to maintain this blind, an otherwise uninvolved 3rd 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 3rd 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 done accurately. |

End of example text

## Study Intervention Compliance

The measures that will be taken to ensure and document intervention compliance should be described (eg, drug accountability records, diary cards, drug concentration measurements, or medication event monitoring). May include the use of electronic data capture.

Consider any implications of under/over dosing and cross reference Section 8.4 if required

## Concomitant Therapy

* Describe which treatments or procedures will be allowed before and during the study and any other specific rules and procedures related to permitted or prohibited concomitant therapy.
* Outline expectations for recording the use of concomitant therapies.
* Mention any non-study treatments, such as background therapy or rescue medication, as applicable.
* 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.
* Consider whether rescue therapy will be allowed and provide details if appropriate.
* Cross reference Appendix X – “Excluded Medications” as applicable.
* Cross reference Appendix X - Medical Device Manual as applicable.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) 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 volunteer studies, consider using the common text beginning 'Participants must abstain from taking prescription...':

Participants must abstain from taking prescription or nonprescription drugs (including vitamins 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 medication may be considered on a case-by-case basis by the [investigator in consultation with the] Medical Monitor [if required].

### Rescue Medicine

If rescue therapy is permitted, consider using the text appearing in section 6.5.1.

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:

1. XXX
2. YYY

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.

## Dose Modification

* Procedures to be used for selecting/modifying each 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 drug/dosage regimen to the use of a specified titration procedure or more elaborate response/toxicity-determined dose modification procedures (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 Withdrawal.
* If dose selection/modification decisions are dependent upon review by a committee, include details in Appendix 3 and make a cross reference here.
* Consider providing information in tabular format for simplicity.

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 also 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 that described for other study participants/cohorts.

OR

If moderate or severe AE are consistently observed across participants in a cohort or if unacceptable pharmacological effects, reasonably attributable to [study intervention] in the opinion of the investigator are observed in more than [X]% of the 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 study 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.

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 pre-specified 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

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

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

## 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

# 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.

## Discontinuation of Study Intervention

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. Specify if participants who discontinue study intervention can or cannot continue the study (ie, continue with study visits).

As appropriate, consider using subheadings.

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

* Liver injury – see libraries for proposed algorithm and text

<Start of common text for liver injury>

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined [in the algorithm] or if the investigator believes that it is in best interest of the participant.

Insert appropriate algorithm from relevant library.

<End of common text>

* Cardiac changes (eg, QTc)

*Insert Library content here*

<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 in the study 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>

* Pregnancy: cross reference Appendix and Section 8.3.5. Pregnancy
* Other safety criteria (eg, AE, PK criteria)
* Disease-state criteria (eg, progressive disease)

*Insert Library content here*

<Start of common text>

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

<End of common text>

### Temporary Discontinuation

### Rechallenge

## Participant Discontinuation/Withdrawal from the Study

Describe the criteria for withdrawal of participants from the study.

<Start of common text>

* A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
* 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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
* 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.

<End of common text>

## Lost to Follow Up

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

<Start of common text>

A participant will be considered lost to follow-up if he or she 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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, he/she will be considered to have withdrawn from the study.

<End of common text>

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

# Study Assessments and Procedures

* Describe the assessments and procedure required during each phase of the study (eg, Screening, Week 1, etc.).
* Give all details that are not obvious from the SoA (eg, time of admission to the study site).
* If the study includes qualitative interviews (or exit interviews), describe these evaluations.
* Specify if the study allows for standard of care procedures as baseline assessments.
* All PRO parameters should be fully integrated into the appropriate sections of the protocol. Separate PRO sections should not be created in the protocol.
* If PRO measures are utilized, include instructions for the investigators regarding the following:
  + Training and instructions provided to participants related to completing the questionnaires.
  + Participant supervision during PRO administration.
  + Timing and order of questionnaire administration during or outside the study visits.
  + 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.
* Details for maximum volume for blood draw, individual blood draws, and volumes required should be included if appropriate to the study.
* If a participant diary (paper or an electronic device) will be used to capture participant- or investigator reported data, then 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.
* Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
* 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 time frame defined 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.

* [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.]

## Efficacy 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.
* Describe methods/training to ensure consistency across centers, use of participant diaries, instructions on timing/conditions of assessment, and if a specifically qualified person (eg, physician, psychologist) should be performing these assessments. Please 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.
* Instructions or protocols for specialized tests may be presented in an appendix; however, do not use copies of case report forms (CRF), published questionnaires, or rating scales as an appendix, as these will need to be redacted before disclosure. Any of these documents utilized 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.
* 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

LEVEL 3 HEADINGS CAN BE ADDED AS REQUIRED.

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 assessment, 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 non-investigator 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 CRF, published questionnaires, or rating scales as an appendix, as these will need to be redacted before disclosure. Any of these documents utilized 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.
* 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.

Planned time points for all safety assessments are provided in the SoA.

### 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
* 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.

### 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.
* [Oral] [Tympanic] [Rectal] [Axillary] [Skin] [Temporal Artery] temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
* 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).
* Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 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 on the CRF.  
  OR  
  Vital signs will be measured in a semi-supine 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 in the CRF.]

### 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 time points 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 factor listed here is consistent with that listed in the QTc exclusion and withdrawal criteria.
* [Triplicate OR Single] 12-lead ECG 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 for [QTc] withdrawal criteria and any additional [QTc] readings that may be necessary.
* At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

### Clinical Safety Laboratory Assessments

* For multicenter studies in participants who are patients, make every effort to ensure routine laboratory safety assessments are performed by a central laboratory. If local laboratory assessments 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 to the SoA for the timing and frequency.
* The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, 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 such 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 assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
  + If laboratory values from non-protocol specified laboratory assessments 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 in the CRF.

<End of common text>

### Suicidal Risk Monitoring

* Clinical trials meeting any of the criteria listed below must employ prospective monitoring of suicidal ideation and behavior:
  + Patient or healthy volunteer studies using study intervention that:
    - Known to be active in the human central nervous system (CNS)
    - Being studied for CNS activity
    - Being developed for any psychiatric or neurologic indication
    - May affect mood, cognition, or behavior via their effects on the CNS (directly or indirectly)
  + Beyond CNS-active study intervention, almost all of which have the potential to affect mood, cognition, or behavior, this category also includes study intervention that are pharmacologically similar to a variety of drugs for which such effects have been reported and are considered to be at least possibly drug-related. Examples include isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss.
  + Studies including any participant population, especially those having an elevated risk of suicidal ideation and behavior which may become manifest during the course of the study, for which the project team feels that monitoring of suicidal ideation and behavior is in the best interest of participant safety or science (eg, new data acquisition). Specify how this determination was made and how the decision/rationale was documented.
  + Single-dose studies in healthy volunteers and studies involving micro-dose level exposure to study intervention for which such pharmacological action is not expected (eg, CNS receptor imaging studies) are exempt.
* Teams should modify the example text to fit their study.
* Consistent with the US-FDA recommendation to use an instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C‑CASA), the recommended instrument is the Columbia–Suicide Severity Rating Scale (C‑SSRS). The FDA has adopted C-CASA as the standard for coding suicidality data.

For studies involving ANY CNS-active study intervention, other than an antidepressant or antiepileptic drug (AED), with product labeling (eg, Warnings & Precautions section of the Global Data Sheet or the Developmental Core Safety Information) that refers to a risk of suicidal ideation or behavior:

Example text:

[STUDY INTERVENTION] is considered to be a central nervous system (CNS)-active. In addition, there have been some reports of [suicidal ideation or behavior as reported in the product label] when it has been given to some participants with [certain conditions]. The sponsor considers it important to monitor for such events before and during this clinical study.

[Include additional 3 common paragraphs noted below.]

End of example text.

For studies investigating ANY CNS-active study interventions (including antidepressants and AEDs being studied in indications other than depression/epilepsy) if suicidal ideation and behavior assessment instruments have been incorporated in the study:

Example text:

[STUDY INTERVENTION] is considered to be an [antidepressant/ antiepileptic/ CNS-active study intervention]. There has been some concern that [antidepressants/ antiepileptics/ some CNS-active study intervention] may be associated with an increased risk of suicidal ideation or behavior when given to some participants with [major depressive disorder/ bipolar disorder/ epilepsy/ certain conditions]. Although this study intervention or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to [healthy volunteers OR this participant population], [the sponsor] considers it important to monitor for such events before or during this clinical study.

[Include additional 3 common paragraphs noted below.]

End of example text

ADDITIONAL COMMON PARAGRAPHS TO BE INCLUDED WITH EACH OF THE EXAMPLES ABOVE:

Example text:

Participants being treated with [STUDY INTERVENTION][COMPARATOR STUDY INTERVENTION] should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing [STUDY INTERVENTION][COMPARATOR STUDY INTERVENTION] in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with [STUDY INTERVENTION][COMPARATOR STUDY INTERVENTION] should be instructed 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 AND/OR treatment-emergent suicidal ideation and behavior] will be [assessed OR monitored] during the study using [NAME OF SCALE]. Refer to [Section X OR Appendix X] for more information.

End of example text

## Adverse Events and Serious Adverse Events

* 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 AE or any planned rechallenge procedures in case study intervention is discontinued because of an AE.
* Consider whether there 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 particular interest it should be described in a subsection (AE of Special Interest). 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?

**NOTE: Level 3 headings** **in this section from 8.3.1 to 8.3.5 are common text and must be maintained in order to ensure the elements required by ICH and regulators are included in the protocol.**

<Start of common text>

The definitions of an AE or SAE can be found in Appendix 3.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 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)

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

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

All AE will be collected from the [signing of the ICF] OR [start of intervention] until [the follow‑up visit] at the time points 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 on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. 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 AE or SAE 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 he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

### Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non‑leading 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 non-serious AEs of special interest (as defined in Section [X]), 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 given in Appendix 3.

### Regulatory Reporting Requirements for SAEs

* Prompt notification by the investigator to the sponsor of a 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 (IRB)/Independent Ethics Committees (IEC), and investigators.
* Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
* An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator’s Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

<End of common text>

### Pregnancy

* Define the time period for collecting pregnancy information for female participants or female partners of male participants as appropriate. This must be consistent with the time period for collecting AEs and SAEs.
* Do not collect pregnancy information for female participants known to be pregnant during the screening phase 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) and any assessments that need to be performed.

<Start of common text>

* Details of all pregnancies in [female participants and, if indicated, female partners of male participants] will be collected after the start of study intervention and until [insert time period that is at least 5 terminal half-lives after the last dose].
* If a pregnancy is reported, the investigator should inform the sponsor within [24 hours] of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
* Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

<End of common text>

### Cardiovascular and Death Events

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

Specify any disease-related events (DREs) and/or disease-related outcomes that do not need to be reported as AEs or SAEs. If DREs are applicable, then include the following wording:

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 a SAE. These events will be recorded on the [corresponding CRF] page in the participant’s CRF within [the appropriate time frame]. [These DREs will be monitored by a/an [independent Data Monitoring Committee, Safety Review Committee, Safety Review Team, other] on a routine basis.]

*NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an 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.*

### Medical Device Incidents (Including Malfunctions)

This section is optional and should be removed if not applicable.

* This section is suggested 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 non-sponsor medical devices, then this section is not needed.
* Instructions for documenting medical device incidents can be provided in Appendix 7.

<Start of common text>

Medical devices are being provided for use in this study [for the purposes of xxxx]. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

#### Time Period for Detecting Medical Device Incidents

* Medical device incidents or malfunctions of the device 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 incident at any time after a participant has been discharged from the study, and such incident 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 Incidents is provided in Appendix 7.

#### Follow-up of Medical Device Incidents

* All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3).This 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 incident.
* New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

#### Prompt Reporting of Medical Device Incidents to Sponsor

* Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
* The Medical Device Incident Report Form will be sent to the sponsor by [method]. If [method] is unavailable, then [alternative method] should be utilized.
* The same individual will be the contact for the receipt of medical device reports and SAE.

#### Regulatory Reporting Requirements for Medical Device Incidents

* The investigator will promptly report all incidents 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 incidents to the IRB/IEC.

<End of common text>

## 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 Investigator’s Brochure.
* Refer the investigator to the approved product label of the comparator (as applicable) for advice on overdose.

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 YYY] and may be used in case of overdose.

<Start of common text>

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until [study intervention] can no longer be detected systemically (at least [x] days).
3. 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).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

<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.
* PK parameters are not evaluated in this study.
* [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 [specify time points only if not obvious from the SoA] A maximum of [X] samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. 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 back-up]). 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.

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

[Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.]

## Pharmacodynamics

* Insert text as appropriate for this study. If pharmacodynamics will be included in the study, provide appropriate text. If not, include a statement to this effect.

Pharmacodynamic parameters are not evaluated in this study.

Include collection of biopsy tissue (archived and fresh), ascites, sputum, bronchial lavage, etc., as appropriate and provide the timing of sample collections relative to study intervention administration, volume of fluid or sample amount required, and any other special instructions. Alternatively, cross reference Section 8.8 Biomarkers.

Venous blood samples of approximately [X] mL will be collected for measurement of [X] at [specify time points only if not obvious in the SoA].

Urine samples will be collected for measurement of [X] at [specify time points only if not obvious in the SoA].

## [Genetics]

* If this will not be part of the study, include a statement to this effect.

Genetics are not evaluated in this study.

* Contact the appropriate sponsor functional area representatives to ensure that appropriate pharmacogenomic 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.

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 X for Information regarding genetic research]. Details on processes for collection and shipment and destruction of these samples can be found in [specify location].

## Biomarkers

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

* Biomarkers are not evaluated in this study.

If biomarkers will be evaluated:

* Include analyses (eg, ribonucleic acid [RNA], serum, plasma, or other soluble markers).
* Indicate any additional analyses, such as flow cytometry, histology, serology, immunogenicity, or histochemical analyses.
* Ensure language describing how long the samples will be stored and how they will be destroyed is included in an ICF and any sample handling manuals.
* If instructions for collection of samples are complex, then consider including them in an appendix rather than the main text of protocol.
* Specify whether optional or required (both here and in the SoA). Required samples must be based on a protocol objective.
* To distinguish between different types of biomarker samples, include the following for each sample, as appropriate:
  + Indicate if residual samples.
  + Indicate the type of sample (eg, serum, plasma, tissue, bone marrow aspirate).
  + Indicate the purpose of the sample (eg, participant eligibility, exploratory research, RNA analysis).
  + Indicate the timing of collection (eg, screening, disease progression); do not give specific time points (eg, Week 4 or Cycle 4) as this information will be provided in the SoA.
  + Indicate the biomarkers that will be studied.
* Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:
  + [blood/saliva]
  + [other required biomarker sample]
* Optional samples for biomarker research that should be collected from participants in the study where possible are the following:
  + [optional biomarker sample]

If specific biomarker sampling is described as a protocol objective, use the suggested text.

* Samples will be tested for [protocol-specific objective] to evaluate their association with the observed clinical responses [protocol-specific response] to [study intervention].

If biomarker work will be done but is not described in the protocol objectives, insert the suggested paragraph. (Note: Ensure that the appropriate ICF is obtained.)

* In addition, samples will be stored and analysis may be performed on biomarker variants thought to play a role in [protocol-specific rationale] including, but not limited to, [specific candidate genes/genome-wide analysis for RNA, serum analytes, or tissue biomarkers] to evaluate their association with observed clinical responses to [study intervention].

If biomarker samples other than pharmacogenetic samples will be collected for analysis not described, consider including the suggested paragraph on how these other samples may be used for research.

Other samples may be used for research to [develop methods, assays, prognostics and/or companion diagnostics] related to [specify the intervention target, disease process, pathways associated with disease state, and/or mechanism of action of the study intervention].

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 biomarker responses to [study intervention].

### Immunogenicity Assessments [If applicable]

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].

### RNA Transcriptome Research [If applicable]

Transcriptome studies [may/will] be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for eachblood and[tissue name]sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to [disease] [and medically related conditions] or the action of [study intervention]*.*

The same samples may also be used to confirm findings by application of alternative technologies.

### RNA Expression Research of a Subset of RNA Species [If applicable]

RNA expression studies [may/will] be conducted using quantitative reverse transcriptase polymerase chain reaction (RT-qPCR), and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in a RNA expression profile for each blood and [tissue name]sample. The RNAs assayed may be those involved with the pathogenesis of [disease]; the absorption, distribution, metabolism, or excretion of [study intervention]; or in the participant’s response to [study intervention]. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to [study intervention] or the pathogenesis of [disease]. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to [disease] [and medically related conditions] or the action of [study intervention].

### Proteome Research [If applicable]

Plasma and [tissue name] proteome studies [may/will] be performed by 2-D gel separation, and/or peptide mass mapping, or an alternative equivalent procedure. Proprietary algorithms and standard statistical techniques, such as analysis of variance (ANOVA) and analysis of covariance (ANCOVA), [may/will] be used to identify individual proteins exhibiting statistically significantly different changes in their levels between samples and/or between groups of samples. These differentially expressed proteins will be identified by mass spectrometry or equivalent technology. This will enable the evaluation of changes in proteome profiles that may correlate with biological response relating to [disease] and medically related conditions or the action of [study intervention].

The samples may also be used to confirm findings by application of alternative technologies.

### Metabolomic Research [If applicable]

[Biofluid name] and [tissue name] metabolome studies [may/will] be performed by nuclear magnetic resonance (NMR), mass spectrometry (MS), liquid chromatography – mass spectrometry (LC-MS), gas chromatography – mass spectrometry (GC‑MS), and/or Fourier transform mass spectrometry (FTMS), and equivalent methods. This may include analysis of identified or uncharacterized metabolites and lipids that are known to be or emerge in the future as important in the pathogenesis of [disease/condition for study intervention] or a related medical condition, the participant’s response to [study intervention], or AE.

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

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

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

* This section does not apply to Patient Reported Outcomes [PROs] (for PROs 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.

[Medical resource utilization] [and] [health economics] data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

* Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
* Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
* Number and type of diagnostic and therapeutic tests and procedures
* Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

# Statistical Considerations

## Statistical Hypotheses

## Sample Size Determination

* State the expected number of participants to be screened, randomized, and expected to be analyzed, including how non completers will be accounted for. For an event driven trial, state the number of events planned along with the number of participants to be randomized. Adapt the text to the study design.
* Ensure evaluable is clearly defined.
* Ensure this section clearly explains how screening failures and non-evaluable participants are defined.
* Provide justification of sample size in accordance with the primary statistical analysis and study objectives.
* Assumptions and methodology for calculations should be provided with references. 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 under-enroll.
* Include power calculations and level of significance to be used as appropriate.
* 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
* Completion of the trial globally is required in order to provide sufficient participants as defined in this section.

Approximately X participants will be screened to achieve X randomly assigned to study intervention and X evaluable participants for an estimated total of X evaluable participants per intervention group.

A maximum of X participants will be randomly assigned to study intervention such that approximately Y evaluable participants complete the study.

## Populations for Analyses

Define analysis populations for this study. Examples are provided in the table. Modify table as needed.

For purposes of analysis, the following populations are defined:

|  |  |
| --- | --- |
| Population | Description |
| Enrolled | [All participants who sign the ICF] |
| Randomly Assigned to Study Intervention |  |
| Evaluable |  |
| Safety | [All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received]. |

## Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

### Efficacy Analyses

|  |  |
| --- | --- |
| Endpoint | Statistical Analysis Methods |
| Primary |  |
| Secondary |  |
| Exploratory | [Will be described in the statistical analysis plan finalized before database lock] |

### Safety Analyses

All safety analyses will be performed on the Safety Population.

|  |  |
| --- | --- |
| Endpoint | Statistical Analysis Methods |
| Primary |  |
| Secondary |  |
| Exploratory | [Will be described in the statistical analysis plan finalized before database lock] |

### Other Analyses

If other analyses are considered primary or secondary, then list them in the efficacy and safety analyses tables in Sections 9.4.1 and 9.4.2. If other analyses are considered exploratory, then use the statement (modify as needed) included in this section.

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

## Interim Analyses

Monitoring of the results of the study should be described. If an interim analysis is planned for a blinded study, describe how a Data Safety Monitoring Board (or other type of assessment committee) will be established to evaluate the interim analyses (the safety data, and/or the critical effectiveness endpoints). Also describe the role of the Data Safety Monitoring Board (for example, to recommend to the sponsor whether to continue, modify, or stop a study).

The following information belongs in this section:

* Reason for conducting interim analyses and their impact on the conduct of the study
* Variables to be included in the interim analyses
* How AEs will be summarized or presented
* The timing of analyses (eg, number of participants entered, number of participants completing certain number of visits, calendar time)
* Any actions resulting from an interim analysis such as sample size re-estimation, stopping rules or any adjustments to nominal significance level for final analyses

[Insert summary of interim analysis]

The Statistical Analysis Plan will describe the planned interim analyses in greater detail

### Data Monitoring Committee (DMC)

# 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 Brochure, 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 the study is initiated.
* 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.
* The investigator will be responsible for the following:
  + 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 (if applicable), and all other applicable local regulations

<End of common text>

### Financial Disclosure

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

[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.]

### Informed Consent Process

<Start of common text>

* The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
* Participants must be informed that their participation is voluntary. Participants or their legally authorized representative [defined as xxx] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 re-consented 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 the participant’s 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.

[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.]

### 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.

* 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 his/her 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.
* The participant must be informed that his/her 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.

### Committees Structure

Optional: 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, Clinical Research Organization). Note that specific details are not required.

### Dissemination of Clinical Study Data

Describe company-specific policy on provision of study results.

For studies conducted in the EU under Regulations EU 536/2014: Consider whether submission of results of the clinical study will be delayed more than one year after the end of the trial and provide substantiated reasons. 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.ClinTrials.gov](http://www.ClinTrials.gov) and other publically-accessible sites.

Publication planning and other activities related to non-promotional, 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.

### Data Quality Assurance

<Start of common text>

* All participant data relating to the study will be recorded on printed or electronic CRF 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.
* The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
* The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
* The sponsor or designee is responsible for the data management of this study including quality checking of the data.
* Study monitors will perform ongoing source data verification 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.
* 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 can be found in [X].

<End of common text>

### Study and Site Closure

<Start of common text>

The sponsor 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:

* 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 recruitment of participants by the investigator
* Discontinuation of further study intervention development

<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.

* 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.

## Appendix 2: Clinical Laboratory Tests

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

Procedure Notes:

* Pregnancy test:
  + Team to decide whether local urine pregnancy testing will be standard for the protocol. Serum testing is mandatory if required by local regulations or the IRB/IEC, or to confirm a positive urine test.
  + As a minimum, a pregnancy test should be performed at screening to confirm absence of pregnancy and at the end of relevant systemic exposure. For studies with interventions with unlikely toxicity, additional pregnancy testing during the clinical study is not necessary.
  + Pregnancy testing should be performed at monthly intervals during studies involving interventions with known or suspected human teratogenicity/fetotoxicity.
  + For studies involving interventions with possible human teratogenicity/fetotoxicity , additional pregnancy testing should be considered. Take into account, among other factors, the duration of the study.
* Hepatitis B and Hepatitis C screening:
  + For Phase I and Phase II 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 III studies, hepatitis testing may not be required unless immunosuppressive agents will be administered. Refer to exclusion criteria for additional guidance.

<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 entered into the CRF.]
* 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.

Table X: Protocol-Required Safety Laboratory Assessments

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Laboratory Assessments | Parameters | | | | | |
| Hematology | Platelet Count | | RBC Indices:  MCV  MCH  %Reticulocytes | | White blood cell (WBC) count with Differential:  Neutrophils  Lymphocytes  Monocytes  Eosinophils  Basophils | |
| Red blood cell (RBC) Count | |
| Hemoglobin | |
| Hematocrit | |
| Clinical Chemistry1 | Blood urea nitrogen (BUN) | Potassium | | Aspartate Aminotransferase  (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT) | | Total and direct bilirubin |
|  | Creatinine | Sodium | | Alanine Aminotransferase  (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) | | Total Protein |
|  | Glucose [Indicate if fasting, or nonfasting] | Calcium | | Alkaline phosphatase | |  |
| Routine Urinalysis | * Specific gravity * pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick * Microscopic examination (if blood or protein is abnormal) | | | | | |
| Other Screening Tests | * Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) * [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] * [Serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)2 * [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 utilized and protocol-required additional local laboratory assessments are needed, include the following: “All study-required laboratory assessments will be performed by a central laboratory, with the exception of “ and list the exceptions. * [All study-required laboratory assessments will be performed by a central laboratory, with the exception of [list the exceptions]: * [SPECIFY REQUIRED TEST(S)]   The results of each test must be entered into the CRF. | | | | | |
| NOTES :  1 Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section [X] and Appendix [X]. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥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 as an SAE (excluding studies of hepatic impairment or cirrhosis).  2 Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. | | | | | | |

Investigators must document their review of each laboratory safety report.

If there are blinded laboratory results:

* Specify analyte(s) results that need to be blinded (eg, hemoglobin A1c [HbA1c]).
* Specify who will be blinded to the data (for example, study team, site).
* Specify when unblinding is appropriate (for example, for safety issues).

[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].

<End of common text>

## Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

<Start of common text>

Definition of AE

|  |
| --- |
| AE Definition |
| * An AE is any untoward medical occurrence in a patient or 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. |

|  |
| --- |
| Events Meeting the AE Definition |
| * 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). * Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. * New conditions 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.   For Events Meeting the AE Definition, use 1 of the 2 example bullets regarding lack of efficacy depending on the type of study. For Phase 1 studies, neither of these examples will be included unless efficacy is an endpoint.  For efficacy studies, use the bullet starting with “Lack of efficacy…”   * "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 fulfil the definition of an AE or SAE.   For non-efficacy studies involving marketed products in established indications use the last bullet.   * The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE. |

|  |
| --- |
| Events NOT Meeting the AE Definition |
| * Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

|  |
| --- |
| A SAE is defined as any untoward medical occurrence that, at any dose: |
| 1. **Results in death** |
| 1. **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 detained (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 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| 1. **Is a congenital anomaly/birth defect** |
| 1. **Other situations:**  * Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events 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 or convulsions that do not result in hospitalization, or development of drug dependency or drug 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 in the CRF. * It is **not** acceptable for the investigator to send photocopies of the participant’s medical records to XXX in lieu of completion of the XXX/AE/SAE CRF page. * There may be instances when copies of medical records for certain cases are requested by XXX. 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 XXX. * 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 1 of the following categories:   * Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. * Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. * Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.   An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.  Other measures to evaluate AEs and SAEs may be utilized (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. * 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. * The investigator will use clinical judgment to determine the relationship. * 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 Product Information, for marketed products, in his/her assessment. * For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. * There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to XXX. 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 XXX.** * The investigator may change his/her opinion of causality in light of follow-up information and send a 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 XXX 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 XXX with a copy of any post-mortem findings including histopathology.] [MAY NOT BE REQUIRED FOR STUDIES WHERE DEATH IS AN ENDPOINT. * New or updated information will be recorded in the originally completed CRF. * The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information. |

Reporting of SAEs

|  |
| --- |
| SAE Reporting to XXX via an Electronic Data Collection Tool |
| * The primary mechanism for reporting an SAE to XXX will be the electronic data collection tool. * If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). * 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 off-line 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 off-line, 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 XXX via Paper CRF |
| * Facsimile transmission of the SAE paper CRF 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 CRF pages within the designated reporting time frames. * Contacts for SAE reporting can be found in [X]. |

<End of common text>

## Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Delete appendix if not required.

<Start of common text>

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

* Documented hysterectomy
* Documented bilateral salpingectomy
* Documented bilateral oophorectomy

Note: Documentation can come from the site personnel’s: review of the participant’s medical records, medical examination, or medical history interview.

1. Postmenopausal female

* A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
* Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male participants

For genotoxic study intervention or for non-genotoxic study intervention with demonstrated or suspected human teratogenicity/fetotoxicity at subtherapeutic exposure levels if relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid to prevent exposure of an embryo/fetus, the following text is required. This text is required ONLY until it has been determined that WOCBP who are partners of male participants no longer need protection from seminal study intervention exposure.

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 5.1]:

* Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table [X] when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition male participants must refrain from donating sperm for the duration of the study and for [X months] after [study completion or the last dose of study intervention].

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile‑vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame].

<End of common text>

Female participants

<Start of common text>

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table [X].

<Start of common text>

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table [X].

<End of common text>

Table [X]: Highly Effective Contraceptive Methods

Table [X]: Highly Effective Contraceptive Methods

|  |
| --- |
| **Highly Effective Contraceptive Methods That Are User Dependent** a  *Failure rate of <1% per year when used consistently and correctly.* |
| * Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulationb   + Oral   + Intravaginal   + Transdermal |
| * Progestogen only hormonal contraception associated with inhibition of ovulation   + Oral   + Injectable |
| **Highly Effective Methods That Are User Independent** a |
| Implantable progestogen only hormonal contraception associated with inhibition of ovulationb   * + Intrauterine device (IUD)   + Intrauterine hormone-releasing system (IUS)   + Bilateral tubal occlusion |
| * **Vasectomized partner**   *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| * **Sexual abstinence**   *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* |
| NOTES:  a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.  b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least [X, corresponding to time needed to eliminate study intervention plus 30 days for study interventions with genotoxic potential]  after the last dose of study intervention |

<End of common text>

Pregnancy Testing:

* Choose from the options for language to be included in the protocol and delete any wording not required
* Decide if local or central testing will be standard for the protocol. Highly sensitive serum testing is mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test.
* As a minimum, a pregnancy test should be performed at the end of relevant systemic exposure. For studies with interventions with unlikely toxicity, additional pregnancy testing during the clinical study is not necessary.
* For studies with interventions or procedures with possible embryo-fetal effects, more frequent pregnancy testing should be considered, taking into account, amongst other factors, the duration of the study.
* WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive [urine or serum] pregnancy test.
* Additional pregnancy testing [should be performed at monthly intervals OR is not required] during the treatment period and at [X, corresponding to protocol-defined time frame in Section 5.1] after the last dose of study intervention and as required locally.
* Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
* Pregnancy testing, with a sensitivity of [5, 10, 25] mIU/mL will be performed [insert any specific information regarding who will perform the test and/or how it will be performed]

Collection of Pregnancy Information:

Male participants with partners who become pregnant

<Start of common text>

* The investigator will attempt to collect pregnancy information on any male participant’s female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive [study intervention].
* After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within [24 hours] of learning of the partner’s pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

<End of common text>

Female Participants who become pregnant

<Start of common text >

* The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within [24 hours] of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
* 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. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
* Any female participant who becomes pregnant while participating in the study [will discontinue study intervention or be withdrawn from the study]

OR

[May request continuation of study intervention]

Continuation of study intervention may only be allowed if either of the following criteria is met:

The study intervention has an approved label that indicates it can be used safely in pregnant females

OR

All of the following apply:

* The participant has a high mortality disease
* The investigator determines the participant is benefitting from study participation and there is no other reasonable treatment for her.
* 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 and the status of the participant and her offspring.
* The protocol is amended to allow such participation on a case-by-case basis, if such participation is not already addressed in the protocol.

<End of common text >

## Appendix 5: Genetics

Delete appendix if not required.

<Start of common 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.
* [INCLUDE FOR DNA COLLECTION WITH PLANNED ANALYSES:] DNA samples will be analyzed for [describe planned analyses]. [Additional] analyses may be conducted if it is hypothesized that this may help resolve issues with 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 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 common text>

## Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]

Delete appendix if not required.

See participant libraries for suggested common text

## Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 which are manufactured by the sponsor or by a 3rd party for the sponsor). If Section 6.1.1 only includes NON-sponsor medical devices or is not applicable, then this appendix is not needed.

<Start of common text>

Definitions of a Medical Device Incident

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).

**Medical Device Incident Definition**

* A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
* Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

**It is sufficient that:**

* An **incident** associated with a device happened.

AND

* The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

* Life-threatening illness
* Permanent impairment of body function or permanent damage to body structure
* Condition necessitating medical or surgical intervention to prevent one of the above
* Fetal distress, fetal death, or any congenital abnormality or birth defects

**Examples of Incidents**

* A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
* A participant’s study intervention is interrupted or compromised by a medical device failure.
* A misdiagnosis due to medical device failure leads to inappropriate treatment.
* A participant’s health deteriorates due to medical device failure.

Documenting Medical Device Incidents

**Medical Device Incident Documenting**

* Any medical device incident occurring during the study will be documented in the participant’s medical records, in accordance with the investigator’s normal clinical practice, and on the appropriate form of the CRF.
* For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3.
* The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee.
* It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
* 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 an incident. This includes any amendment to the device design to prevent recurrence.

<End of common text>

## Appendix 8: Country-specific Requirements

Delete appendix if not required.

## Appendix 9: Abbreviations

* Generate a list while drafting the protocol to reflect the abbreviations used in the protocol.
* Only include those that are used more than once in the document. Once a term is abbreviated, it should be abbreviated in the rest of the document.
* Abbreviations are defined where first used in the document. If suggested text contains an abbreviation, the author can choose to retain the abbreviation or substitute the whole word(s).
* Delete appendix if not required.

## Appendix 10: Protocol Amendment History

Delete appendix if not required.

<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 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**

[Rationale]

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

<end of common text>

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

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 drugs in a higher age range for this patient population

|  |  |  |
| --- | --- | --- |
| **Section # and Name** | **Description of Change** | **Brief Rationale** |
| 6.1. 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 convention published by the International Committee of Medical Journal Editors [ICMJE, 1991]. 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).

Example of a reference:

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