Title Page

Protocol Title:

<Start of suggested text>

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

<End of suggested text>

Consider if specifying 'Sex' is necessary for the study, if not a specific requirement, consider inclusive language/terminology. This link provides Sexual orientation and Gender Identities (SOGI) terms and definitions.

Protocol Number: [protocol number]

Amendment Number: [amendment number]

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

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

Compound: [number or name]

Brief Title:

<Start of suggested text>

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

<End of suggested text>

Study Phase: [study phase]

[Acronym]:

Sponsor Name:

Legal Registered Address:

[Manufacturer]: [insert manufacturer]

Regulatory Agency Identifier Number(s):

Registry	ID

[Pediatric Investigational Plan Number]

Approval Date:

Sponsor Signatory:

[Name]	**Date**
[Title]	

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

Protocol Amendment Summary of Changes Table

<Start of common text>

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

Amendment [X] (Day-Month-Year)

<End of common text>

<Start of suggested text>

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].

<End of suggested text>

<Start of common text>

Overall Rationale for the Amendment:

[INSERT rationale statement]

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

<End of common text>

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List of Abbreviations [and Definitions of terms]

<Start of suggested text>

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

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

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

<End of suggested text>

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Ensure wording here matches the title page. **Brief Title:**

Ensure wording here matches the title page. **Regulatory Agency Identifier Number(s):**

Registry ID

[Pediatric Investigational Plan Number]:

Rationale:

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
•	•
Secondary	
•	•

Overall Design Synopsis:

<Start of suggested text>

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

<End of suggested text>

Brief Summary:

<Start of suggested text>

Is this a study focused on a specific disease, disease pathway, or intervention? If yes, the burden and epidemiology of the disease should be described. Further, any unmet medical need or needs of the population and or subgroup should be described here. If possible, a design that offers remote or flexible visit options wherever possible is encouraged.

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

Study details include:

- The study duration will be up to [numerical value, eg, days, weeks, months].

- The treatment duration will be up to [numerical value, eg, days, week
- The visit frequency will be [X].

<End of suggested text>

During the design phase, the study should consider features that enable ease of access to trial including possibility of doing virtual visits, weekend hours, using local labs or home health care for visits, if possible, to allow those who may have challenges with transportation, job or childcare. Visit frequency should be minimized to the extent possible consistent with the study goals.

Number of Participants:

<Start of suggested text>

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

A maximum of [X] participants will be [enrolled / randomiz d to investiga intervention]

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

<End of suggested text>

Will the study include defined subgroups based on demographics of disease or the intended population of the intervention? If so, reference to the subgroups should be described here.

Study Arms and Duration:

Data Monitoring/Other Committee: [Yes/No]

<Start of suggested text>

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

<End of suggested text>

While not part of the written protocol, attention to diversity of the membership serving on the DMC and other committees should be considered.

1.2. Schema

Will the study include defined subgroups based on demographics of disease or the intended population of the intervention? If so, reference to the subgroups should be described here.

1.3 Schedule of Activities (SoA)

Procedure	Screening (up to [X] days before Day 1)	Intervention Period [Days or Weeks, etc]									E/D	Follow-up ([X] days after last dose)	Notes E/D = Early Discontinuation
		–1	1	2	3	4	5	6	7	8			
Informed consent	X												
Inclusion and exclusion criteria	X												[Recheck clinical status before randomization and/or first dose of investigational intervention.]
Demography	X												
Full physical examination including height and weight	X												
Medical history (includes substance use [and family history of premature CV disease])	X												Substances: [drugs, alcohol, tobacco, and caffeine]
Current medical conditions	X												
[Highly sensitive serum OR urine] pregnancy test (WOCBP only)	X	X											s]
[HIV, Hepatitis B and C screening]	X												
Laboratory tests (include liver chemistries)	X	X					X			X			

Does the study exclude participants based on these factors? If so, exclusion should be scientifically, medically or ethical justified. Unnecessary exclusion of populations is unethical. Recent FDA guidance provides direction for cancer trials for people with HIV, Hepatitis B and C, for example.

Procedure	Screening (up to [X] days before Day 1)	Intervention Period [Days or Weeks, etc]									E/D	Follow-up ([X] days after last dose)	Notes E/D = Early Discontinuation
		–1	1	2	3	4	5	6	7	8			
12-lead ECG	X		X		X				X	X			
Vital signs	X	X	X	X	X	X	X	X	X	X			
[Randomization] if applicable		X											
Genetic sample			X										ICF for genetic sampling should be added per sponsor process (e.g., part of ICF or separate ICF).
Study intervention			X						X				
AE review		X	←==========→										
[Solicited administration-site events if applicable]			←==========→								X	X	[Pain, redness, or swelling]
[Unsolicited AEs if applicable]		X	←==========→								X	X	See Appendix 3 for definitions

Procedure	Screening (up to [X] days before Day 1)	Intervention Period [Days or Weeks, etc]									E/D	Follow-up ([X] days after last dose)	Notes E/D = Early Discontinuation
		–1	1	2	3	4	5	6	7	8			
SAE review		X	←==========→								X	X	
[Device deficiencies if applicable]		X	←==========→								X		
Concomitant medication review		X	←==========→								X	X	
[Study-specific assessments (eg, PK, efficacy)]													

If possible, the following elements should be included and addressed. Return of aggregate study results, Return of individual research results and assessment of eligibility for post-trial access to intervention.

When applicable, include Patient Reported Outcomes (PROs) to be inclusive of the patient voice/experience, and to further inform the trial and its design.

2. Introduction

<Start of example text>

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

<End of example text>

2.1. Study Rationale

2.2. Background

The protocol should include background information regarding what is known of the epidemiology of the disease, its impact and pathway, the population(s) and demographics of the populations affected, any variability in safety/efficacy/other by subgroup, and available drugs and/or intervention(s) for treatment by subgroup, if known. This information should be linked to the study rationale as relevant. Is the intended accrual population aligned with the demographics of the disease, including the incidence and severity, of the population for whom the intervention is intended, or of the general population in the region?

<Start of example text>

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

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

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

<End of example text>

2.3. Benefit/Risk Assessment

Are certain subpopulations at greater risk or potential benefit than others? If so, how, and why? What is this study doing to reduce burden and risk, and safeguard protections for those most vulnerable, understudied, or underrepresented? Will the study impact health equity or disparity for individuals, communities or other groups?

<Start of suggested text>

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

<End of suggested text>

2.3.1. Risk Assessment

As applicable, include potential risk by demographic subgroups. In addition, factors relating to social determinants of health (SDOH) may need to be listed with potential mitigation strategies for risk reduction.

2.3.2. Benefit Assessment

2.3.3. Overall Benefit Risk Conclusion

<Start of example text>

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

<End of example text>

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
•	•
Secondary	
•	•
[Tertiary/Exploratory/Other]	
•	•

Add patient reported outcomes of relevance to participant populations and subgroups.

[Primary estimand / coprimary estimands / Multiple primary estimands]

<Start of example text>

The primary clinical question of interest is:

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

The estimand is described by the following attributes:

Include subgroup considerations.

- *Population:*

  [patients with [condition/disease]/individuals]
- *Endpoint:*

  change from baseline to [timepoint] in [health measurement/outcome]
- *Treatment condition:*

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

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

  difference in mean changes between treatment conditions

Rationale for estimand: [rationale].

<End of example text>

Include subgroup considerations.

Secondary estimand(s)

<Start of example text>

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

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

Include subgroup considerations. A secondary endpoint should include a statistical analysis of subpopulations if enrollment is sufficient.

The estimand is described by the following attributes:

- *Population:*

  Patients with [condition/disease]

- *Endpoint:*

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

Include subgroup considerations.

- *Treatment condition:*

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

- *Remaining intercurrent events:*

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

- *Population-level summary:*

  Difference in proportion of patients with response

Include subgroup considerations.

Rationale for estimand: [rationale]

<End of example text>

4. Study Design

Does the overall study question and study design address the diversity of the population and potential subgroup differences for which the product is intended (e.g., ancestry, comorbidities etc.)?

4.1. Overall Design

4.2. Scientific Rationale for Study Design

4.2.1. Patient Input into Design

Ensuring a diverse, representative, and inclusive participant and community voice is essential to the success of the study. This section should include how participants and/or community input was sought, collected, and included in the design of the study.

- How did input/feedback from the community and potential participants inform the study?
- How was representativeness of that input and feedback considered?

4.3. Justification for Dose

<Start of suggested text>

For this device, the term *dose* refers to [insert as appropri

<End of suggested text>

Does the protocol application include information about prior dosing, PK or PD studies, approved or tested, in previously studied populations by demographic (e.g., subgroups)? This information will address differences among subgroups and populations.

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

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

OR

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

OR

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

OR

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

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

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

OR

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

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

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

4.4. End-of-Study Definition

<Start of suggested text>

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

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

<End of suggested text>

5. Study Population

<Start of common text>

Prospective approval of protocol deviations to recruitment and enrollmer
protocol waivers or exemptions, is not permitted

<End of common text>

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the follo

Age

<Start of suggested text>

1. Participant must be [18] [or the legal age of consent in the jurisdiction in which the study is taking place] to [X] years of age inclusive, at the time of signing the informed consent.

End of suggested text>

Type of Participant and Disease Characteristics

Start of suggested text>

2. Participants who are overtly healthy as determined by medical evaluation including [medical history, physical examination, laboratory tests, and cardiac monitoring].
3. Participants who are [insert criteria]

<End of suggested text>

Weight

<Start of suggested text>

4. Body weight within [insert range including units] and BMI within the range [X – X] kg/m^2 (inclusive)

<End of suggested text>

Sex and Contraceptive/Barrier Requirements

5. [male and/or female]

<Start of common text>

Contraceptive use by [men and women] should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants:

Female participants:

<End of common text>

Does the protocol application provide a detailed explanation on the intended population that is based on the general populations' demographic distribution, the epidemiology of disease, those expected to receive the intervention, and/or by any other demographic distribution? These should be characterized and elucidated in as much detail as possible here. Additional guidance is provided in the NIH policy on Inclusion, and FDA guidance on Enhancing Diversity in Clinical Trial Population.

- A planned demographic table should be included here.

Does the protocol (or an ancillary document) include a Recruitment Plan that details where and how potential participants will be recruited? Is there a description of culturally and linguistically appropriate materials that will be used to recruit participants?

- See RSD document from MRCT toolkit

Are all inclusion criteria scientifically, medically, and/or ethically grounded and valid? Are inclusion criteria adjusted for laboratory and other differences by subgroup of study population?

Is there a strong scientific and/or ethical rationale to exclude pediatric populations? Exclude adolescents? How has the given lower age limit been decided?

Is there a strong scientific and/or ethical rationale to exclude participants above a certain age? Are there less restrictive alternatives to exclusion?

Does the protocol include provisions for accommodation or adjustments for different populations, such as:
a. individuals with disabilities
b. individuals at the extremes of weight
c. individuals whose preferred language is other than English (or the preferred language of the region)
d. individuals who are gender diverse

Does the protocol make appropriate considerations and exceptions around body weight and BMI if they are part of the inclusion/exclusion criteria?
Is BMI eligibility criteria justified based on scientific, medical, and/or ethical evidence?

Consider the inclusion of transgender participants and capturing their gender appropriately.
Consider if knowledge of hormonal therapy may be necessary for the study.
If contraception is required, are there accommodations for religious beliefs?
Are privacy and confidentiality protections in place for adolescents who may be sexually active?

Informed Consent

<Start of common text>

"Signing" should be inclusive of accommodations for those with disabilities, including physical, expressive, and other conditions. Accommodations (e.g., supported decision-making, legally authorized representative) for individuals with cognitive and intellectual impairment should be considered. Specified language requirements (e.g., "read speak or write English") must be scientifically defended.

6. 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>

Inclusion criteria should be as broad as possible within safety parameters.

Other Inclusion Criteria

7.

Are all exclusion criteria scientifically, medically, or ethically justified? The justifications should be explicit and included in the protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. [ ]

Prior/Concomitant Therapy

2. [ ]

Prior/Concurrent Clinical Study Experience

3. [ ]

Diagnostic Assessments

4. [ ]

Do reference intervals and normal values for routine laboratory tests consider race, ethnicity, geography, sex, age, weight, BMI so as not to exclude subgroups unnecessarily and inappropriately?

Other Exclusion Criteria

5. [ ]

5.3. Lifestyle Considerations

Are lifestyle considerations presented in a culturally considerate and inclusive way for all potential participants? Lifestyle considerations may include diet, physical activity, religious or other cultural practices etc. Participants should not be excluded because of their language ability or preference, cultural or religious beliefs and practices, socioeconomic status, and other factors.

- [ ]
- [ ]

5.3.1. Meals and Dietary Restrictions

<Start of suggested text>

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

<End of suggested text>

5.3.2. Caffeine, Alcohol, and Tobacco

<Start of suggested text>

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

<End of suggested text>

5.3.3. Activity

<Start of suggested text>

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

<End of suggested text>

5.3.4. Other Restrictions

5.4. Screen Failures

Detail how screen failures will be reviewed to determine if some subgroups are excluded more than others. Examining screen failure rates and data are important to determine if there is selection bias and whether the resulting data is representative. If investigators need additional resource to track screen failures, a Screen Failure Tracking Log can be found here.

<Start of suggested text>

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

<End of suggested text>

<Start of suggested text>

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

<End of suggested text>

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

6. Study Intervention(s) and Concomitant Therapy

<Start of common text>

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

<End of common text>

6.1. Study Intervention(s) Administered

Table 1. Study Intervention(s) Administered

Intervention Label				
Intervention Name	[Generic (or trade name if required) as per CMC, if applicable, or sponsor number]	[Generic (or trade name if required) as per CMC, if applicable, or sponsor number]	[Placebo]	[Any additional products provided as part of the study
Intervention Description	[eg, dosage form, dosage, frequency]	[eg, dosage form, dosage, frequency]	[eg, dosage f… …quency]	
Type	[drug/device/biologic]	[dr… …ice/biologic]	[drug/device/biologic]	[drug/device/biologic]
Dose Formulation	[tablet/ampule/capsule]	[tablet/ampule/capsule]	[tablet/ampule/capsule]	[tablet/ampule/capsule]
Unit Dose Strength(s)	[dose strength of the product ie, each unit]	[dose strength of the product ie, each unit]	[dose strength of the product ie, each unit]	
Dosage Level(s)	[dose amount and frequency]	[dose amount and frequency]	[dose amount and frequency]	frequency]
Route of Administration	[oral/IM/IV infusion/IV injection]	[oral/IM/IV infusion/IV injection]	[oral/IM/IV infusion/IV injection]	[oral/IM/IV infusion/IV injection]
Use	[experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other]	[experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other]	[experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other]	[experimental, placebo, active comparator, sham comparator, rescue medication, background intervention, challenge agent, diagnostic, or other]
IMP and NIMP/AxMP.	IMP or NIMP	IMP or NIMP	IMP or NIMP	IMP or NIMP
Sourcing	[Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer]	[Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer]	[Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer]	[Insert/modify as appropriate: Provided centrally by the sponsor or locally by the study site, subsidiary, or designee. If device, list manufacturer]

Are pediatric formulations included as an alternative (for either age-appropriate use or for individuals with disabilities)?

Are any modifications of dose levels required for any subgroup included in the protocol?

Packaging and Labeling	Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement.	Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement.	Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement.	Study intervention will be provided in [container]. Each [container] will be labeled as required per country requirement.
[Current/ Former Name(s) or Alias(es)]	Current/former name(s) or alias(es)	Current/former name(s) or alias(es)	Current/former name(s) or alias(es)	Current/former name(s) or alias(es)

Table 2. Study Arm(s)

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

Instructions should be provided in plain language, with appropriate design and imagery, and translated to be culturally and linguistically appropriate for the populations recruited. Instructions should be available in alternative formats to accommodate individuals with disabilities.

6.1.1. Medical Devices

<Start of suggested text>

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

<End of suggested text>

6.2. Preparation, Handling, Storage, and Accountability

<Start of common text>

1. The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator, [institution, the head of the medical institution (where applicable), or authorized site staff] is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the [study reference manual or other specified location].

<End of common text>

6.3. Assignment to Study Intervention

<Start of example text>

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

<End of example text>

6.4. [Blinding, Masking]

<Start of example text>

Type of Study	*Example text to use*
Open-label, no blinding at site level	*This is an open-label study; potential bias will be reduced by the following steps: [central randomization, adjudications].*
Open-label using central randomization via IVRS/IWRS	*This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by the following steps: [central randomization, adjudications].*
Blind break (IVRS/IWRS)	*This is a double-blind study in which [participants/care providers/investigators/outcomes assessors, etc] are blinded to study intervention. The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.*
Open-label using blinded randomization	*This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using randomization envelopes. The site will receive blinded randomization envelopes that will be opened in ascending numerical order immediately prior to the start of study intervention administration for each participant. The site will record the date and time the envelope was opened.*

Blind break (envelopes)	*This is a double-blind study in which [participants/care providers/investigators/outcomes assessors, etc] are blinded to study intervention. A sealed envelope that contains the study intervention assignment for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the sponsor.*
Blinded study with unblinded third party who is dispensing intervention	*Participants will be randomly assigned in a [1:1] ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.* *This third party will instruct the [participant/participant's parent(s) or legally authorized representative] to avoid discussing the taste, dosing frequency, or packaging of the study intervention with the investigator.* *In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.*

<End of example text>

<Start of suggested text>

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

<End of suggested text

6.5. Study Intervention Compliance

<Start of suggested text for studies using bulk supplies>

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

<End of suggested text for studies using bulk supplies>

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

Consider alternative compliance measures for decentralized or hybrid clinical trials that are generally less burdensome for participants.

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

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

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

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

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

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

Throughout this section, attention should be paid to subgroup representation in PK PD studies and other dosing decisions. Diverse representation should be affirmatively planned.

6.6. Dose Modification

<Start of suggested text>

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

<Start of suggested text>

6.6.1. Retreatment Criteria

<Start of suggested text>

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

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

- [Criterion 1]
- [Criterion 2]

<End of suggested text>

6.7. Continued Access to Study Intervention after the End of the Study

6.8. Treatment of Overdose

<Start of suggested text>

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

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

<End of suggested text>

<Start of common text>

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

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

<End of common text>

6.9. Prior and Concomitant Therapy

<Start of suggested text>

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

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

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study

intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

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

<End of suggested text>

6.9.1. Rescue Medicine

<Start of suggested text>

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

- [X]
- [X]

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

<End of suggested text>

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

<Start of common text>

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

<End of common text>

7.1. Discontinuation of Study Intervention

<Start of suggested text>

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

<End of suggested text>

7.1.1. Liver Chemistry Stopping Criteria

<Start of common text for liver injury>

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

<End of common text for liver injury>

7.1.2. QTc Stopping Criteria

<Start of common text for cardiac changes>

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

<End of common text for cardiac changes>

7.1.3. Temporary Discontinuation

7.1.4. Rechallenge

7.1.4.1. Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

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

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

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

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

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

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

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

Refer to Appendix 6 Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Restart/Rechallenge Guidelines] for details on the [restart/rechallenge] process.

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

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

7.2. Participant Discontinuation/Withdrawal from the Study

<Start of common text>

- A participant may withdraw from the study at any time at the participant's own re
for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator f
safety, [behavioral, or compliance] reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation v
should be conducted, as shown in the SoA. See SoA for data to be collected at the
study discontinuation and follow-up and for any further evaluations that need to b
completed.
- The participant will be permanently discontinued from the study intervention and
study at that time.

The protocol application should provide a plan to review participant discontinuation / withdrawal, by demographic and other non-demographic factors. Examining discontinuation / withdrawal rates and data are important to determine if there is a pattern to withdrawal. Further, it is important to assess whether there is selection bias influencing the generalizability of the results.

The reason for withdrawal should be documented, including the specific behaviors or compliance concerns that led to withdrawal by the investigator. If it's a sponsored trial, the sponsor should review and document.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

<End of common text>

The protocol application should provide a plan to review participant loss-to-follow-up, by demographic and non-demographic factors. Examining discontinuation / withdrawal rates and data are important to determine if there is a pattern to withdrawal. Further, it is important to assess whether there is selection bias influencing the generalizability of the results.

7.3. Lost to Follow up

<Start of common text>

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes 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 equivalent methods). These contact attempts should be documented in the participant medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- [Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.]

Consider alternative methods to "visit" (e.g., video-conferencing, home visiting nurse, local laboratory) for decentralized or hybrid clinical trials that are generally less burdensome for participants.

<End of common text>

Consider including: 'Procedures for return of urgent (and other) results to the participant and/or their health care provider and referral for further medical care have been anticipated and planned, and consent obtained.'

8. Study Assessments and Procedures

<Start of common text>

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

<End of common text>

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

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

8.1. Administrative [and General/Baseline] Procedures

8.2. [Efficacy and/or Immunogenicity] Assessments

Planned timepoints for all [efficacy and/or immunogenicity] assessments are provided in the SoA.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

<Start of suggested text>

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

<End of suggested text>

8.3.2. Vital Signs

<Start of suggested text>

- [Oral] [Tympanic] [Rectal] [Axillary] [Skin] [Temporal artery] temperature, pulse rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed [specify participant's position, if applicable] with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- For blood pressure measurements, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure readings will be recorded.
- Vital signs will be measured in a [specify participant's position, if applicable] position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse [and respiratory rate]. [Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.]

<End of suggested text>

8.3.3. Electrocardiograms

<Start of suggested text>

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

<End of suggested text>

Consider including: 'Procedures for return of results to the participant and/or their health care provider have been anticipated and planned, and consent obtained. Referral for further follow up medical care has been considered.'

8.3.4. Clinical Safety Laboratory Tests

<Start of common text>

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

<End of common text>

8.3.5. Pregnancy Testing

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

<Start of example text>

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

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

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

<End of example text>

<Start of suggested text>

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

a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

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

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

<End of suggested text>

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

<Start of common text>

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

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

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

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

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

8.4.1. 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 study intervention] until [the follow-up visit] at the timepoints specified in the SoA (Section 1.3).

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

Questions should be asked in the preferred language of the participant, or through an interpreter if needed.

8.4.3. Follow-up of AEs and SAEs

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

<End of common text>

8.4.5. Pregnancy

Throughout this section, consider referencing “individuals able to give birth” and “their partners,” rather than specifying any sex or gender.

<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 [time period for reporting pregnancies should align with the time period for postintervention contraception determined in Section 5.1].

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor [within 24 hours] of learning of the [female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner)] pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The [participant/pregnant female partner] will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the [participant/pregnant female partner] and the neonate and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former [study participants/pregnant female partner], 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] [may request continuation of study intervention.]

Consider changing the language to be more inclusive, recommend using **they, their, and them.**

<End of common text>

<Start of suggested text>

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

- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

<End of suggested text>

8.4.6. Cardiovascular and Death Events

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

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

- [Event A

- Event B
- Event C
- Event D]

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded within [the appropriate timeframe]. [These DREs will be monitored by a/an [independent data monitoring committee, safety review committee, safety review team, other] on a routine basis. See Section 10.1.5]

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

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

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

8.4.8. Adverse Events of Special Interest

8.4.9. Medical Device Deficiencies

<Start of common text>

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

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

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

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

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

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

8.4.9.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.

- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

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

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

<End of common text>

8.5. Pharmacokinetics

<Start of suggested text>

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

<End of suggested text>

<Start of suggested text>

- [Plasma/serum/whole blood/urine] samples of approximately [X] mL will be collected for measurement of [plasma/serum/whole blood/urine] concentrations of [study intervention/other] as specified in the SoA (Section 1.3) [specify timepoints only if not obvious from the SoA].
- A maximum of [X] samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the PK of [study intervention]. Each [plasma/serum/whole blood] sample will be divided into [X] aliquots (1 each for [PK, other analyses, and a backup]). Samples collected for analyses of [study intervention (plasma/serum/whole blood)] concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these [plasma/serum/whole blood] samples [unless consent for this was included in the informed consent]. Participant confidentiality will be maintained. At visits during which [plasma/serum/whole blood/etc] samples for the determination of [multiple aspects] of [study intervention] will be taken, one sample of sufficient volume can be used.
- Intervention concentration information that [may/would] unblind the study will not be reported to investigative sites or blinded personnel [until the study has been unblinded].

<End of suggested text>

8.6. Pharmacodynamics

8.7. Genetics

If genetic samples are being collected, the importance of a diverse and representative population should be appreciated. The informed consent form can include an affirmative statement to explain the necessity of adequate representation and how patient confidentiality and privacy will be protected. Further, that results of exploratory genetic studies will/will not be returned to participants.

<Start of suggested text>

Genetics are not evaluated in this study.

<End of suggested text>

<Start of suggested text>

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

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

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

<End of suggested text>

8.8. Biomarkers

<Start of suggested text>

Biomarkers are not evaluated in this study.

<End of suggested text>

<Start of suggested text>

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

<End of suggested text>

The informed consent form should explain, in language understandable to the participant, that results of exploratory studies and/or biomarkers will or will not be returned to participants.

8.9. Immunogenicity Assessments

<Start of suggested text>

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

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

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

<End of suggested text>

8.10. [Health Economics OR Medical Resource Utilization and Health Economics]

<Start of suggested text>

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

<End of suggested text>

<Start of suggested text>

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

The data collected will

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

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

<End of suggested text>

9. Statistical Considerations

The statistical analysis plan should include whether and how subgroup population differences will be evaluated and reported. Consider alternative statistical approaches (e.g., Bayesian analyses). Consider descriptive reporting even if study is not powered for full analysis.

<Start of example text>

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

<End of example text>

<Start of suggested text>

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

<End of suggested text>

9.1. Statistical [Hypothesis/Hypotheses]

<Start of example text>

Example 1:

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

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

vs.

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

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

Secondary objective [1]:

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

Secondary objective [2]:

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

Example 2:

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

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

Noninferiority (noninferiority margin is [noninferiority margin])

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

The rationale for the non-inferiority margin is…

Superiority

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

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

<End of example text>

9.1.1. Multiplicity Adjustment

<Start of example text>

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

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

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

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

The steps in the hierarchical testing procedure are as follows:

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

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

<End of example text>

9.2. Analysis Sets

<Start of example text>

Example 1:

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

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

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

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

Example 2:

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

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

PAS : participant analysis set

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

Example 3:

The following participant analysis sets are defined:

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

The following data points sets are defined:

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

DPS: Data Points Set

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

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

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

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

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

<End of example text>

9.3. Statistical Analyses

A clear and comprehensive statistical analysis plan should be presented here. Section 9.3.6 requests information for subgroup analysis; it is important to determine if/when heterogeneity of treatment may exist and which analyses are needed in such instances.

9.3.1. General Considerations

9.3.2. Primary [Endpoint(s)/Estimand(s)] Analysis

Patient-centered endpoints should be included (e.g., cancer patients may be more concerned about energy, vitality, and quality of life, in addition to tumor shrinkage and remission).

9.3.2.1. Definition of endpoint(s)

9.3.2.2. Main Analytical Approach

9.3.2.3. Sensitivity [Analysis/Analyses]

9.3.2.4. Supplementary [Analysis/Analyses]

9.3.3. Secondary [Endpoint(s)/Estimand(s)] Analysis

9.3.4. [Tertiary/Exploratory/Other] [Endpoint(s)/Estimand(s)] Analysis

9.3.5. [Other] Safety Analyses

9.3.6. Other Analyses

<Start of example text>

Subgroup analyses of the primary endpoint and confirmatory secondary endpoints will be made to assess consistency of the investigational intervention effect across the following subgroups:

- *Age group: < 65 vs ≥ 65 years*
- *Sex: female vs male*
- *Race: white vs black vs. other*

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. The analyses will be conducted using a test for heterogeneity and results will be presented on forest plots presenting the estimated study arm difference and 95% confidence intervals. Further details on the statistical analysis will be provided in the SAP.

<End of example text>

9.4. Interim [Analysis/Analyses]

<Start of example text>

An interim analysis of the primary endpoint will be performed by the independent data monitoring committee (IDMC), consisting of [X] clinicians and 1 statistician who are independent experts not

otherwise involved in the study when approximately [X] primary events have occurred. The analysis method for the primary efficacy endpoint described in Section 9.3.2 Primary Endpoints/Estimands will be used for the interim analysis. Based on the group sequential design with the [O'Brien Fleming] alpha spending approach, a 2-sided alpha of [X] will be allocated to the interim analysis. In addition, if the conditional power for the final analysis (based on the original assumption for the remaining study) is [X] or lower, the study may be stopped for futility.

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

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

<End of example text>

9.5. Sample Size Determination

<Start of example text>

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

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

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

<End of example text>

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

<Start of common text>

10.1.1. Regulatory and Ethical Considerations

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

<End of common text>

10.1.2. Financial Disclosure

<Start of suggested text>

[Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.]

<End of suggested text>

The ICF form should be available in a language understandable to the participant. Certified translations and interpreter services should be available for people who may not be able to read or understand the English consent form. The budget should anticipate additional interpreter costs to the study. Accommodations for people with disabilities should be anticipated.

10.1.3. Informed Consent Process

<Start of common text>

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

The ICF form should be available in the participant's or LAR's preferred language.

<End of common text>

<Start of suggested text>

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

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

[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.]

<End of suggested text>

10.1.4. Recruitment strategy

10.1.5. Data Protection

<Start of common text>

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

<End of common text>

<Start of suggested text>

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

<End of suggested text>

10.1.6. Committees Structure

10.1.6.1. [Early Safety Data Review AND/OR Committee]

<Start of suggested text>

- Participant safety will be continuously monitored by the [sponsor's internal or external] [safety review or insert others] committee, which includes safety signal detection at any time during the study.
- In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to [study intervention] administration. An initial safety review for this study is planned for the first [X participants/X% of participants] who are dosed and have provided safety data for [X] days after administration of Dose [X].
- All safety data collected will be summarized and reviewed by the [sponsor's internal/external safety review or other committee] for agreement of next steps.
- In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a requirement to [pause/stop] the study.
    - [Any deaths, regardless of causality]

  - [Any vaccine-related SAEs]
  - [Grade 3 fever reported in more than 2 participants (see table in Appendix [3/7])]
  - [Other]

- [Enrollment will be paused during the review]. If a [pausing/stopping] rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.
- Case unblinding may be performed for above reviews if necessary.

<End of suggested text>

10.1.7. Dissemination of Clinical Study Data

10.1.8. Data Quality Assurance

<Start of common text>

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in [specify location of information].
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- [Quality tolerance limits (QTLs) will be predefined in the [state location(s)] to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.]
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the [monitoring plan] [contracts].
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for [X] years after study completion unless local regulations or institutional policies require a longer retention period. No records may be

destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

<End of common text>

10.1.9. Source Documents

Self-reported data about race/ethnicity and other demographic and non-demographic factors should be reconciled with data in the CRF forms to ensure congruency.

<Start of common text>

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

<End of common text>

10.1.10. Study and Site Start and Closure

First Act of Recruitment

<Start of suggested text>

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

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

<End of suggested text>

Study/Site Termination

<Start of common text>

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

The reasons for termination should be explained to the participant in language understandable to them, provisions for follow up in the event of late potential adverse events should be made in addition to follow up care. The IEC/IRB should review the plans for currently enrolled participants as well as information planned to be provided to those who have completed all study-related procedures.

<End of common text>

10.1.11. Publication Policy

<Start of common text>

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

<End of common text>

Include when and how participants will be provided with plain language summaries and how the community and the public will be informed of aggregate results of the study.

The normal values (e.g., BMI, HgA1c, blood pressure, hemoglobin, white blood cell count, creatinine clearance etc.) should account for known variations in different subgroups. The subgroup specific normal values should be included in the eligibility criteria and appropriately documented. This may require a conversation with the central lab on how this is monitored and applied correctly.

10.2. Appendix 2: Clinical Laboratory Tests

<Start of common text>

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

Table X: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	• Platelet count	
	• Red blood cell (RBC) count	
	• RBC indices	– Mean corpuscular volume (MCV) – Mean corpuscular hemoglobin (MCH) – %Reticulocytes
	• White blood cell (WBC) count with differential:	– Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
	• Hemoglobin • Hematocrit	

Normal WBC levels, for instance, should be adjusted for race and ethnicity.

Normal hemoglobin levels, for instance, should be adjusted for age, sex, race, and ethnicity.

Clinical chemistry[1]	• Blood urea nitrogen (BUN) • Potassium • Creatinine • Sodium • Calcium • Glucose [indicate if fasting or nonfasting]	• Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) • Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Alkaline phosphatase[2] • Total and direct bilirubin • Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leu by dipstick • Microscopic examination (if blood or protein is abnormal)	
Pregnancy testing	• Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]	
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • [Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] [or specify other tests] [if applicable] • [All study-required laboratory tests will be performed by a central laboratory, with the exception of [list the exceptions]: ○ [SPECIFY REQUIRED TEST(S)]	

Throughout this section, consider referencing "individuals" rather than specifying any sex or gender.

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section [7.1.1 Liver Chemistry Stopping Criteria] and Appendix [6: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]]. All events of ALT [or AST] ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT [or AST] ≥3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to [sponsor] in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. 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.

<End of common text>

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

<Start of common text>

10.3.1. Definition of AE

AE Definition

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

Definition of Unsolicited and Solicited AE

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition

- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- [Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.]
- [The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.]

Events <u>not</u> Meeting the AE Definition

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

10.3.2. Definition of SAE

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

a. Results in death

b. 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation

and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. [Is a suspected transmission of any infectious agent via an authorized medicinal product]

g. Other situations:

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

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [X] to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- [If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide [X] with a copy of any postmortem findings including histopathology.]
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to [X] within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

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

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

SAE Reporting to [X] via Paper Data Collection Tool

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

<End of common text>

10.4. Appendix 4: Contraceptive and Barrier Guidance

<Start of common text>

10.4.1. Definitions

<End of common text>

10.4.2. Contraception Guidance

10.5. Appendix 5: Genetics

<Start of suggested text>

Use/Analysis of DNA

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

<End of suggested text>

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Restart/Rechallenge Guidelines]

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

<Start of common text>

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

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

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

10.7.2. Definition of Medical Device SAE, SADE and USADE

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

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
- A permanent impairment of a body structure or a body function.

- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

d. [Is a suspected transmission of any infectious agent via a medicinal product]

SADE definition

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

Unanticipated SADE (USADE) definition

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

10.7.3. Definition of Device Deficiency

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

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

Medical Device AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to [X] in lieu of completion of the [X]/AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by [X]. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to [X].

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

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

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

Assessment of Causality

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

investigator always make an assessment of causality for every event before the initial transmission of the SAE data to [X].

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [X] to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- [If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide [X] with a copy of any post-mortem findings including histopathology.]
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to [X] within 24 hours of receipt of the information.

10.7.5. Reporting of Medical Device SAEs

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

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

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

- [Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the [X/medical monitor/SAE coordinator]].

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

10.7.6. Reporting of SADEs

SADE Reporting to [X]

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

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

<End of common text>

10.8. Appendix 8: Country-specific Requirements

10.9. Appendix 9: Protocol Amendment History

<Start of common text>

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

Amendment [amendment number]: ([date])

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.

Overall Rationale for the Amendment

[Rationale]

Section # and Name	Description of Change	Brief Rationale

<End of common text>

<Start of example text>

Amendment 3: 30 March 2016

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

Overall Rationale for the Amendment

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

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

Example of Numbering Global and Country-specific Protocol Amendments

Type of Protocol Amendment	*Numbering*	*Type of changes*
Country-specific	*Amendment 3/FRA-2*	*Same changes specific to France added to global Amendment 3 (no new changes for France)*

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

Example of Numbering a Site-specific Protocol Amendment

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

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

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

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

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

<End of example text>

11. References

<Start of example text>

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

<End of example text>